The Journal of Pediatrics

VOL. 28 JANUARY, 1946 No. 1

Original Communications

EPIDEMIC POLIOMYELITIS

LOUIS P. GEBHARDT, PH.D., M.D., AND WILLIAM M. MCKAY, M.D., C.P.H.
SALT LAKE CITY, UTAH

THE disease poliomyelitis is endemic in many parts of the United States throughout the year, but epidemic periods usually are evident by June or July, the peak being in August or September with a beginning decline by October. In the warmer climates of the United States, the disease may show an upward swing as early as April, as was the case in the Los Angeles area during the 1943 epidemic. This general cycle of endemicity and epidemic peaks is repeated regularly with moderate to severe epidemics being prevalent every four to six years, with a general regional variation in the United States.[1]

The diseases transmitted by direct contact, such as meningococcus meningitis, whooping cough, measles, and mumps are more prevalent in the late fall, winter, and spring months. Such disease agents are more frequently spread from person to person by nasopharyngeal droplets. In contrast, poliomyelitis is a summer or late summer and early fall disease, with peaks more akin to those of enteric diseases or to the morbidity of insect born diseases. Enteric diseases, such as typhoid fever and dysentery, may, however, become epidemic in any month if a water or food supply is contaminated, and these epidemic peaks are frequently reached with explosive suddenness. A recent fly-borne epidemic of *Shigella paradysenteriae* Boyd 88 was reported by Kuhns and Anderson.[2] No flies were observed in the bivouac area prior to September 1. Flies began to appear and as the epidemic increased, great numbers were present. A total of 1,557 cases were reported from September 1 to the first week in October. The morbidity decreased with a decrease in fly population. The specific organisms producing the disease were isolated from several samples of flies trapped near the encampment.

Poliomyelitis cases, on the other hand, generally increase more gradually, the epidemic peak coming in late August or September, depending upon the area. In the poliomyelitis epidemic of 1943, in California, the following monthly cases were reported: April, 27; May, 43; June, 181; July, 380; August, 506; September, 590; October, 269; November, 204; and December, 69. There is then

From the Department of Bacteriology, School of Medicine, University of Utah, and the State Department of Public Health.

These studies were supported by the University of Utah Research Committee Fund.

a fairly abrupt falling off of cases in October with only a few appearing as late as December.

Poliomyelitis is also characterized, in many instances, by sporadic and isolated cases, with several spotted cases in various suburban as well as urban areas during an epidemic. Likewise, there is a paucity of cases among closely associated groups, such as schools, orphan homes, or nurseries. It seems, therefore, that if this disease were strictly a contact disease there should be more cases in these latter groups as is the case with strictly contact diseases.

Various opinions have been advanced as to the reason for the seasonal incidence of epidemic poliomyelitis, with suggestions as to the mode of spread of the disease. Direct contact spread via the nasopharynx has been suggested by Flexner,[3] Schultz and Gebhardt,[4] Aycock,[5] and others. Water supplies have been suggested as a vehicle by which virus may be spread (Kling,[6] Toomey,[7] and others). A few small epidemics have been proved to have been milk-borne (Knapp, Godfrey, and Aycock,[8] Aycock[9]). Food contaminated with virus has also been suggested as a possible means by which the disease agent gains entrance to the body (Toomey and August,[10] Toomey,[11, 13] and Barber[12]).

Virus has been isolated from stools of patients with active cases of the disease and convalescents as well as from the stools of carriers who have had no evidence of the disease clinically.[14-18] The virus has also been isolated from sewage during nearly every month of the year.[19-21]

The possibility of insect transmission of the virus has gained momentum in the past few years, since the virus has been isolated from several species of flies (Paul and associates,[22] Sabin and Ward,[23] Trask and associates,[24] Sabin and Ward[25]).

EPIDEMIOLOGICAL SURVEY

Previous to 1943, the greatest number of cases reported in the State of Utah was 109 in 1939, but in 1943 there were 400 cases in the State.

During late August and early September, 1943, the disease reached epidemic proportions, with 43 cases in August and 211 cases during September. A survey was therefore begun in an attempt to find, if possible, something in common with all or a high percentage of the cases of the disease. The following possibilities were considered as means by which the virus may be spread from one individual to another: direct contacts, water supplies, swimming pools, insect bites, milk supplies, and food supplies.

CONTACTS

Actual contacts with diseased patients were very few, and patients developing the disease after exposure from five to twenty-five days with a known case of poliomyelitis showed only 33 cases of 241 surveyed, or 13.6 per cent, possible direct contact infections.

The Salt Lake City Public Schools were to have started their fall term Sept. 8, 1943, but due to the poliomyelitis epidemic students from kindergarten to the sixth grade were not allowed to attend school. Students from the seventh grade through high school attended school September 8, 9, and 10. The complete school system was then ordered closed until September 27.

During the month of August, there was a total of six cases of poliomyelitis in Salt Lake City in children from the age of 6 to 17 years. This was during the time when no school was in session. During September while schools were closed, there were thirty-five cases of poliomyelitis in the same age groups, 6 to 17 years. During October there were twelve cases of poliomyelitis in Salt Lake City in this age group or a decided decline in the number of cases after school reopened. These figures, therefore, correlate the epidemic trend in the State, irrespective of school association. (See Graph 1.)

After reopening the schools,* September 27, 29,099 students returned to school. By October 1, 30,351 students had returned; by October 20, 31,243 students had returned. It was, therefore, not until this latter date that the total enrollment had returned to school. Many parents kept their children from school after reopening, fearing that they might contract the disease.

From the data given, it would appear that children are just as safe in school as they are out of school. It also fails to reveal any increase in the number of cases of the disease with a reopening of school, with "contacts" greatly increased in the schoolroom as well as on the playground.

Two isolated cases suggested that means other than direct contact may play a role in the spread of the disease. One case, J. J. W., a 3½-year-old girl, developed the disease at a sheep camp, seventy miles from the nearest inhabitant. This child came to town during the summer only about one day each month with the family to purchase supplies. The family lives in this town during the winter and spring months. This child came to their home and remained in town one day, twenty-seven days previous to developing the disease. There were no poliomyelitis cases during 1943 in the town where the family normally lived, and to the knowledge of the mother, the child had contacted no one with even a suspicion of any disease. Foodstuffs, including fresh fruits and vegetables, were taken back with them to the camp as supplies. The only inhabitants of the camp were the father, mother, and the child.

The other case, G. A., a 13-month old male, lived in a small town of 473 inhabitants. This child went to the outskirts of a city 101 miles distant, with his mother, two weeks previous to his developing poliomyelitis. They contacted no one; the mother picked apples from an orchard and then came home. The farm from which the apples were obtained was located in a fairly extensive epidemic area. None of three sisters, who remained at home, ranging in age from 5 to 11 years, developed any illness whatsoever. The three sisters did not eat any unwashed fruits except peeled ones, while the baby, on two known occasions, had played with and had bitten into several unwashed apples obtained from the epidemic area. There were no other cases of poliomyelitis in this town or even in neighboring towns, fifty or more miles distant.

The only possible thing in common in these two isolated cases was fresh fruit—"apples." Both children had nibbled at or had eaten unwashed, unpeeled apples, from one to two weeks previous to developing the disease.

*Arthur E. Arnesen, Supervisor of Curriculum and Research, The Board of Education of Salt Lake City, Utah: Personal communication.

WATER SUPPLIES

The diversity of water supplies, including springs, dug wells, drilled wells, and artesian wells, suggested that water supplies were not incriminated in the spread of the virus during this epidemic. Even the water supply of Salt Lake City is not from one single source, but from several sources, with separate storage reservoirs and distributing systems for different areas of the city. Cases of the disease were too scattered to consider any given water supply as a source of virus.

MILK SUPPLIES

Milk supplies for the various villages, towns, and cities came from variable sources, and no direct connection of cases of the disease with any single or multiple milk sources could be traced. The family cow, neighbors' cows, milk from first-class dairies, and from well-regulated processing and pasteurizing plants, all supplied milk, and no correlation between cases and milk supplies could be elicited in 241 cases of the disease surveyed.

SWIMMING POOLS

Of 241 interviews with persons having poliomyelitis, eleven, or 4.1 per cent, had been in swimming from five days to two weeks previous to developing the disease. The swimming pools varied from creeks, irrigation ditches, and farm ponds to regulation swimming pools. The variable areas of these water sources for swimming failed to reveal any connection of disease spread by such contact.

INSECT BITES

Of 241 cases surveyed, 105 persons, or 43.5 per cent, gave histories of being bitten by mosquitoes or flies from five days to two weeks or more before developing the disease. However, in over one hundred normal persons surveyed in the same areas, about the same percentage revealed mosquito or fly bites. These included normal sisters, brothers, mothers, and fathers of patients with poliomyelitis, as well as children with no family history of the disease.

FOODSTUFFS

No attempt was made to determine the kinds of cooked or prepared foods eaten by the children who developed poliomyelitis. Only raw, uncooked, and unwashed types of foodstuffs were considered as a possible source of virus, since heating to 60° C. for a few minutes destroys the virus. Therefore, the field was narrowed to fresh uncooked foodstuffs.

In many instances parents were insistent that all fresh fruits and vegetables eaten by the child who had developed the disease were washed or peeled. On closer questioning, nearly all the parents admitted that the child had eaten unwashed or unpeeled fresh fruits or vegetables. In other instances, if the child were old enough to question, he admitted eating raw unwashed fruits or vegetables, even though previously the parents insisted all foodstuffs of this nature had been washed or peeled. Pride of parents often was a stumbling block, and an "I don't remember" answer was frequent.

Of a total of 206 cases of poliomyelitis surveyed, 192 persons, or 93.2 per cent, had eaten unwashed or unpeeled fresh fruits one to two weeks or more previous to developing the disease. Among the fresh fruits more commonly eaten were apples, peaches, and pears. Less commonly eaten were cherries, grapes, apricots, and plums. Strawberries were eaten unwashed only rarely, due primarily to the high cost and to the fact that this foodstuff was kept out of reach of children prior to preparation for eating.

Of this same group (206 cases), 140, or 67.9 per cent, also ate fresh, unwashed or unpeeled vegetables. Tomatoes led the list of such vegetables. Raw celery and carrots were less frequently eaten by the persons surveyed.

A combination of the two categories, unwashed or unpeeled fresh fruits and vegetables, shows that 206 out of 206, or 100 per cent, of the patients with poliomyelitis in the survey had eaten these foods one to two weeks or more prior to developing the disease.

The only foods found in common in all of the cases of the survey were therefore, fresh fruits and vegetables. This in itself would not lend too much evidence as a possible means of spread of the virus if other data failed to dovetail, since it is frequently a common practice for children to eat raw unwashed fruits and vegetables. Such data, however, appear to fit into the jigsaw puzzle of epidemic poliomyelitis.

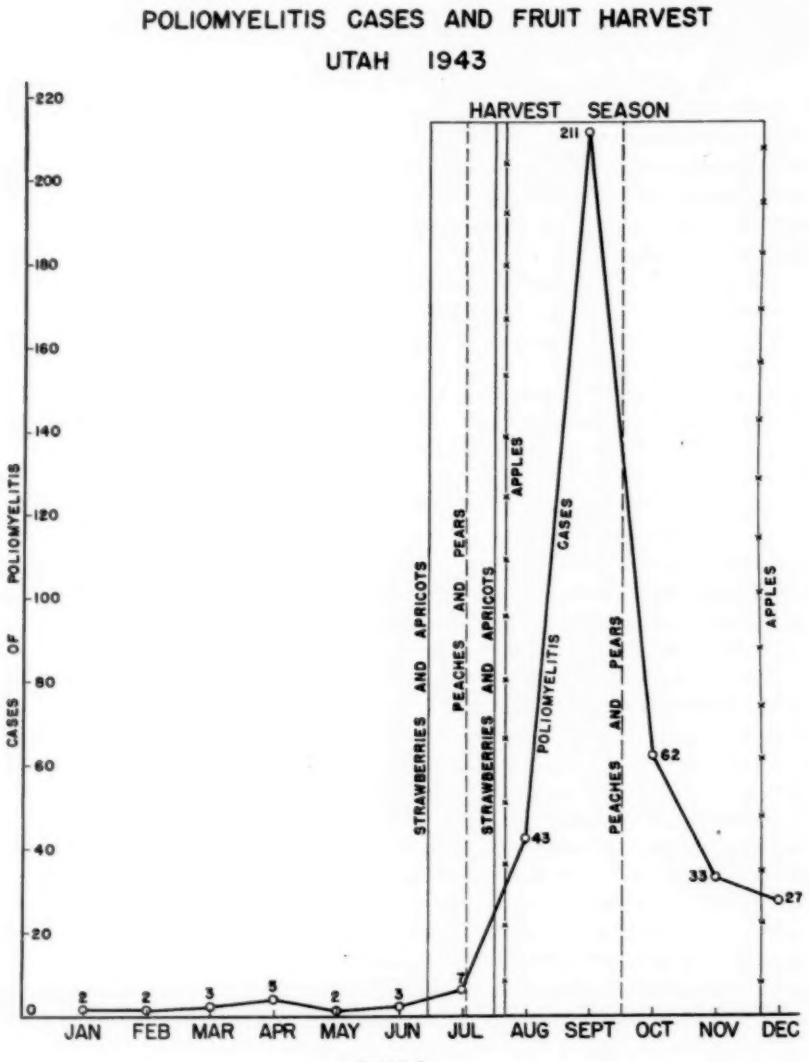
COMPARISON OF FRUIT AND VEGETABLE HARVEST WITH PEAK POLIOMYELITIS CASES

It has been previously suggested by Toomey[10, 13] that epidemic poliomyelitis may bear some relationship to the peak harvest of fresh fruits. He also suggested that the incidence of flies was greater during the harvest peak, particularly during the fruit seasons. No explanation was offered, however, as to how fruits may be a transfer agent for this virus.

From the data collected, it is noted that peach, pear, and apple production peaks, particularly,[26, 27] closely parallel epidemic poliomyelitis case peaks (Graph 1). From this graph it is shown that such edible fruits as strawberries and apricots in Utah begin to ripen in June and are usually off the market by the end of July or the first part of August. The number of cases of poliomyelitis in June, 1943, was 3; in July, 7. In Utah, beginning the middle of July, peaches and pears begin to ripen with peak ripening periods in August, but continue through September. Poliomyelitis cases in August were 43. Apple ripening in Utah begins in early August, continuing through November, with peak ripening in September and through October. The tomato season is from August through October, with a September peak production. The total cases of poliomyelitis in Utah in September, 1943, was 211; October, 62; November, 33; December, 27. In other states, during 1943, this same trend is evident.

In the State of New York, in 1943, the number of cases rose from 3 in May to 20 in June and then 36 in July. In August 132 cases were reported and in September 300, the case peaks paralleling harvest peaks.[26-28] Strawberries and cherries both begin to ripen in June, the former carrying through the latter part of July with cherries extending beyond the end of August. Peaches begin

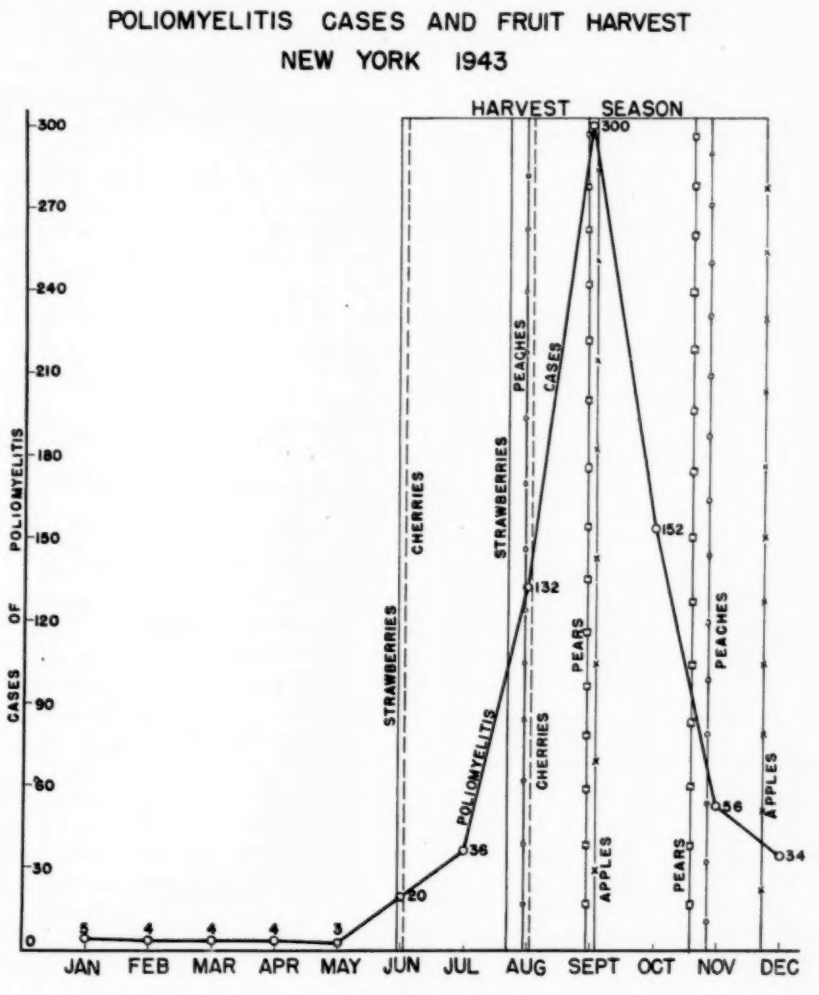
to ripen the latter part of July and the first week in August, continuing through October. Pears and apples begin to ripen the latter part of August and the first week of September and carry through early fall. Graph 2 shows the relationship.



Graph 1.

In California,[26, 27] if fresh fruits and vegetables were in some way responsible for the carriage and dissemination of virus, one would expect an earlier appearance of an epidemic. Likewise, a greater number of cases should be maintained at or near the peak than in states with a shorter and less varied fruit and

vegetable season. Graph 3 shows this relationship. The epidemic in California was suggested as early as April, with 27 cases; in May, 43 cases were reported; June, 181; July 380 (Contrast this with 36 cases in July in the State of New York); August, 506; September, 590; October, 269; November, 204; and December, 69. What relationship, then, does the spread of poliomyelitis virus have

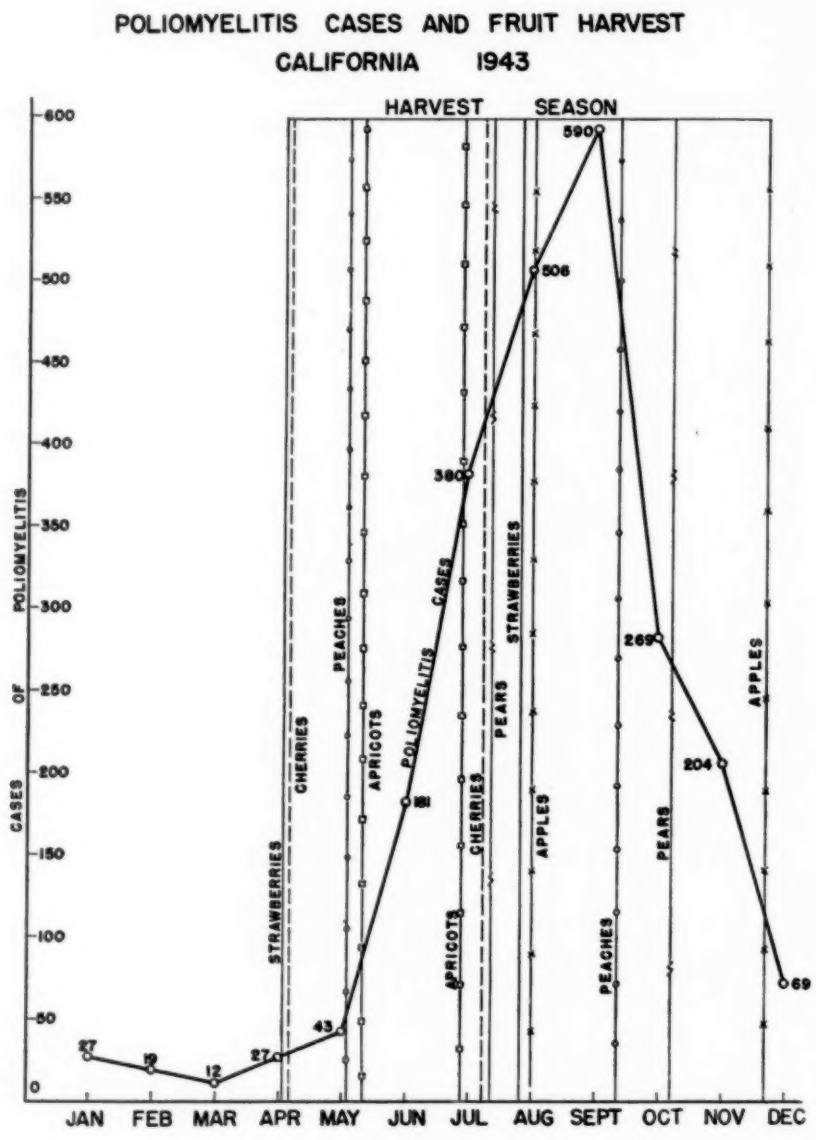


Graph 2.

to fruit or vegetables? How do such edible foods become contaminated? Why should children be affected more frequently with this disease?

It has already been shown by several investigators that certain flies may harbor the virus of poliomyelitis. It has also been shown that sewage is an

excellent source of the virus. Thus, flies obtaining virus from sewage might easily deposit fecal material containing the virus on fruits and vegetables. Fresh fruits and vegetables are invariably exposed to flies both in the field and on vegetable and fruit stands as well as on peddlers' trucks. Virus containing



Graph 3.

fly feces deposited on such foodstuffs would, therefore, offer a "virus source" to be ingested by susceptible individuals. If such foodstuffs are unwashed, virus may be taken into the mouth when these foods are eaten. Passage of "natural sewage or fecal virus" through flies may enhance its virulence* or increase its quantity. If the fly population is high and ample sewage virus available, the probability of more flies being carriers of virus seems possible.

It is conceivable that of a given group of foodstuffs, only a few units may be contaminated, or, on the other hand, if many units are contaminated, the virus may be more widely distributed. In the former, only a single unit may have been contaminated by fly feces, and thus only one person of a family unit may obtain the virus. Since children from 2 to 15 years of age are not usually particular about "washing" such raw foodstuffs, this age group would be more likely to become infected. Also the more active child is more prone to get into such foods unobserved. Likewise, if subinfecting quantities of virus are deposited, the person ingesting the virus may well have no effects or at the most only very mild, subclinical symptoms, resulting in an immunity. If many units of foodstuffs are contaminated by fly feces virus, many cases of the disease will be evident, if sufficient virus is deposited on the foodstuff to produce infection. Thus, if a given family obtains such contaminated foodstuffs, more than one family member, if susceptible, will develop the disease, or harbor the virus in their nasopharynx or in the feces. Multiple cases in such a family would, therefore, develop the disease or symptoms at or about the same time. This fact is suggested by a study of multiple cases in families.

MULTIPLE CASES IN FAMILIES

From the data presented in Table I, 45 multiple cases in 20 families show that the development of the disease was, in 32 of the cases, on the same day or within zero to five days after the brother or sister developed poliomyelitis. The longest interval between family cases was 61 days; the shortest interval between family cases was zero days (12 cases). It is, therefore, highly probable that the majority of these multiple cases obtained their infection from a common source and at about the same time.

It is suggested that members of a given family unit, mother, father, and siblings, may all harbor the virus of poliomyelitis in their feces at or about the same time, but only one member may exhibit symptoms of the disease.[29] The virus is, therefore, probably more widely distributed in family groups than was previously thought. The family unit, therefore, undoubtedly obtains the virus from a common source and the probability of "contact" of all members with another human case or carrier of the virus at the same time does not seem entirely reasonable.

PREVALENCE OF FLIES

Many species of flies were prevalent in Utah in 1943 in fairly great numbers, and during August and September swarms of flies were in evidence. It was not difficult to trap several hundred of several different species in a single day.

*In this laboratory, it has been demonstrated that the Vi antigen of *Eberthella typhosa* increases slightly on fly passage.

TABLE I. MULTIPLE CASES OF POLIOMYELITIS IN FAMILIES IN UTAH, 1943

FAMILY	CASES PER FAMILY (NO.)	DATES OF ONSET	INTERVAL IN DAYS BETWEEN CASES IN SAME FAMILY
1	2	July 15	
		July 15	0
2	2	Aug. 1	
		Aug. 13	12
3	2	Aug. 13	
		Aug. 20	7
4	3	Aug. 16	
		Aug. 20	4
		Aug. 23	3 (7)*
5	2	Aug. 24	
		Aug. 24	0
6	4	Aug. 29 (two)	0 (two)
		Aug. 31 (two)	2 (two)
7	3	Aug. 27	
		Sept. 1	4
		Sept. 7	6 (11)*
8	2	Sept. 2	
		Sept. 3	1
9	2	Aug. 3	
		Sept. 9	36
10	3	Sept. 3	
		Sept. 8	5
		Nov. 8	61
11	2	Sept. 4	
		Sept. 11	7
12	2	Sept. 6	
		Sept. 8	2
13	2	Sept. 10	
		Sept. 12	2
14	2	Sept. 10	
		Sept. 14	4
15	2	Sept. 14	
		Sept. 14	0
16	2	Sept. 15	
		Sept. 15	0
17	2	Oct. 4	
		Oct. 4	0
18	2	Oct. 15	
		Oct. 20	5
19	2	Oct. 16	
		Nov. 11	26
20	2	Nov. 25	
		Nov. 26	1

*Longest interval in days between first and last case where there were more than two cases per family.

Likewise, hand-netting produced an abundant catch. Flies became numerous the latter part of July and continued to be fairly numerous to the middle of November. A few *Phormia regina* were trapped in lecture rooms and laboratories, during the winter of 1943-1944, at which time the outside temperature ranged from –1 to +10 degrees F.

The following species of flies were trapped* and identified:† *Phormia regina*,‡ *Lucilia sericata, Calliphora erythrocephela, Fannia canicularis, Fannia scalaris, Musca domestica,* and *Muscina stabulans. Fannia canicularis* were

*Flies were trapped or hand-netted and a preliminary identification was made by Mr. Dan Oniki, Department of Biology, University of Utah.

†Final identification of flies was made by Dr. David T. Jones, Associate Professor, Department of Biology, University of Utah.

‡In a single experiment laboratory bred *Phormia regina* flies fed "virus bearing" sewage, possessed the virus of poliomyelitis in the feces, collected (pooled) ten to fifteen days after feeding. Other similar experiments have thus far been negative for virus.

trapped both inside and outside of buildings and as the usual incidence, males predominated inside. However, outside catches revealed a fairly high percentage of female *F. canicularis* in 1943.

In 1944, however, when a total of only twenty-four cases of poliomyelitis was reported in Utah, flies were comparatively scarce. It was difficult to trap a hundred flies, and this took several days unless baited areas were used such as garbage cans, decayed meat, or other similar places. It is also of interest to note that during 1944 the male to female ratio of *F. canicularis,* trapped out of doors, was 293 to 2. If flies are responsible for the dissemination of virus, the female may, for some reason, play a more important role than the male. The quantity of available food influences the ratio of males to females, and with abundant food females are about 2 to 1 more prevalent (Hermes[30]).

In one small peach orchard located in a small town and surveyed in September, 1943, thousands of flies of several species were swarming about the fallen fruit. Likewise, in the same month, a small apple orchard ten miles distant from the peach orchard was found to be literally swarming with flies. Both orchards were frequented by many children ranging from 3 to 15 years of age. Eight cases of poliomyelitis were near these areas. These same orchards, in 1944, revealed very few flies during either August or September. In a home near (two hundred yards) this apple orchard, three children in one family developed the disease, all three having frequented this orchard and eaten fallen unwashed fruit, one to two weeks or more previous to developing poliomyelitis. No known contacts with cases of poliomyelitis could be traced in this group of cases.

RELATIONSHIP OF OPEN PRIVIES AND DRAINS TO POLIOMYELITIS CASES

In one city of 5,214 inhabitants, surveyed[31] for open privies and drains, it was found that in the eastern section, sewage facilities were undeveloped. There were thirty-two open privies and drains from waste disposal units. In this section, there have been thirteen cases of poliomyelitis. In the southern section outside the city limits, where no sewage system exists, five cases of poliomyelitis have been reported. In the north and west sections, which have adequate sewage systems, no cases have been reported. Several small orchards are located near these areas.

In another city of 2,733 inhabitants, 13 cases of poliomyelitis developed during 1943. This is a morbidity rate of 468, which is nearly eight times the *State* morbidity rate of 61.5 for the same year. The sewage disposal units in this city consist of open privies, cesspools, and septic tanks. Open ditches containing raw sewage are prevalent.

Great swarms of flies were present in this area in August, September, and October, 1943, but flies were quite scarce during the same period in 1944. Traps baited with decaying meat, fruit, and human feces failed to net more than forty to fifty flies in several five-day periods of collection in the above locality during the above three months in 1944.

DISCUSSION

The data presented in Table I point to other means than contact as the mode of spread of this disease. Twelve multiple cases of poliomyelitis developed in six families on the same day; twenty multiple cases developed from one to

five days after onset of the disease in a brother or sister and ten of these cases developed within two days of that of the siblings. Of a total of forty-five multiple cases in families, thirty-two developed in less than the generally accepted incubation period of from seven to fourteen days after exposure, if we consider the brother or sister to expose another member of the family. In one family with four cases, two children developed the disease the same day and two developed the disease two days after. Two other children, who had played with those in the family with four multiple cases and had eaten of the same unwashed peaches, apples, and pears on Aug. 17 and 18, 1943, developed the disease August 31 and September 1, respectively, or about the same time that the multiple cases of the disease (four in one family) had developed. This data therefore suggests that the majority of these patients were exposed to the virus at about the same time and probably from the same source. No direct contacts with any known cases of poliomyelitis and the multiple cases could be traced, except the family unit and the two cited cases of patients who developed the disease at the same time as the four children in the other family.

This is in contrast with multiple cases in families having a well-known contact disease such as measles, mumps, or chicken pox, where a brother or sister generally develops the disease after the regular incubation periods, when secondary cases in families develop.

Possible common virus sources for these multiple cases of poliomyelitis in families could be virus contaminated foodstuff, since all members of a given family unit usually eat the same kind of food.

Peak fruit and vegetable production and highest fly incidence correlate the peak period of poliomyelitis cases and the evidence presented that 100 per cent of the persons in the cases surveyed had eaten unwashed or unpeeled fresh fruits and vegetables from one to two or more weeks prior to developing poliomyelitis, suggests that foods may play a role in the dissemination of the virus. Ample virus source could well be represented in areas of faulty sewage disposal and with swarms of flies present, virus-to-fly-to-food-to-patient seems to be in the realm of probability. Such foods that may be contaminated with the virus find their way into many different areas, including remote and isolated places, which would account for isolated and sporadic cases of the disease.

It is suggested, therefore, that poliomyelitis is an accidental disease of the "filth borne" group of diseases; that "virus contaminated food" may play a very active role in the spread of this disease. The limitations of spread of the virus would be dependent on fly population, source of virus for flies, and an adequate source of fresh foods, such as fruits and vegetables, as well as other foods that may be eaten uncooked. Also that such foods be convenient to populated areas in order for virus, that may be deposited, to survive for a sufficiently long enough time to be ingested by susceptible individuals.

Definite proof of the spread of virus of poliomyelitis by means of contaminated food rests on actually isolating the virus from fresh foodstuffs and demonstrating that flies may contaminate such foods by depositing virus thereon. Such proof has been suggested by Ward and associates[32] since they were able to isolate the virus from bananas contaminated by flies.

SUMMARY

1. Multiple cases of poliomyelitis in families show that the majority of the cases developed at the same time. Also that in these multiple cases the children probably obtained the virus at the same time and from the same source, suggesting means other than contact as the mode of spread.

2. Fresh unwashed or unpeeled fruits and vegetables were eaten in 206 of the 206 cases of poliomyelitis surveyed.

3. Direct contact was traced in only 13.6 per cent of the 241 cases surveyed.

4. No evidence was found that water supplies, milk supplies, or swimming pools were means by which the disease was disseminated.

5. Bites of insects, such as flies and mosquitoes, suggests a possible means of virus spread.

6. Closing of schools during the epidemic failed to reduce the incidence of the disease among the school age group.

The authors wish to express their appreciation for the co-operation of: Mrs. Dorothy Lowman, Director, Utah State Public Health Nurses; State, County and City Public Health Nurses; W. V. Hickey, Chief Sanitarian, Salt Lake City; Elmer B. Quist, State Sanitarian; Howard M. Hurst, State Sanitary Engineer; and Dr. D. Keith Barnes, State Public Health Officer.

REFERENCES

1. Dauer, C. C.: Pub. Health Rep. 58: 937, 1943.
2. Kuhns, Dwight, M., Colonel, M. C., and Anderson, Theodore G.: Am. J. Pub. Health 37: 750, 1944.
3. Flexner, S.: Am. J. Dis. Child. 9: 353, 1915.
4. Schultz, E. W., and Gebhardt, L. P.: Proc. Soc. Exper. Biol. & Med. 30: 1010, 1933.
5. Aycock, W. L.: Harvard Symposium, Cambridge, Mass., 1940, Howard University Press, p. 556.
6. Kling, C.: Bull. Off. Mt. Hyg. Publ. 20: 1799, 1928.
7. Toomey, J. A.: J. PEDIAT. 19: 103, 1941.
8. Knapp, A. C., Godfrey, E. S., Jr., and Aycock, W. L.: J. A. M. A. 87: 635, 1926.
9. Aycock, W. L.: Am. J. Hyg. 7: 791, 1927.
10. Toomey, J. A., and August, M. H.: Am. J. Dis. Child. 46: 262, 1933.
11. Toomey, J. A.: J. PEDIAT. 8: 664, 1936.
12. Barber, G. O.: Brit. M. J. 2: 1137, 1938.
13. Toomey, J. A., Takacs, W. S., Tischer, L. A.: J. PEDIAT. 23: 168, 1943.
14. Sawyer, W. A.: Am. J. Trop. Dis. & Prev. Med. 3: 164, 1915.
15. Toomey, J. A.: J. A. M. A. 109: 402, 1937.
16. Trask, J. D., Vignec, A. J., and Paul, J. R.: J. A. M. A. 111: 6, 1938.
17. Howe, H. A., and Bodian, D.: J. Infect. Dis. 56: 198, 1940.
18. Lipine, P., Sedallian, P., and Sautter, V.: Bull. Acad. de Méd., Paris 122: 141, 1939.
19. Foreign News Letters, Paris, J. A. M. A. 114: 2232, 1940.
20. Trask, J. D., and Paul, J. R.: Am. J. Pub. Health 31: 239, 1941.
21. Paul, J. R., and Trask, J. D.: J. A. M. A. 116: 493, 1941.
22. Paul, J. R., Trask, J. D., Bishop, M. B., Melnick, J. L., and Casey, A. E.: Science 94: 395, 1941.
23. Sabin, A. B., and Ward, R.: Science 94: 590, 1941.
24. Trask, J. D., Paul, J. R., and Melnick, J. L.: J. Exper. Med. 77: 531, 1943.
25. Sabin, A. B., and Ward, R. W.: Science 95: 300, 1942.
26. War Food Administration, Food Distribution Administration, August, 1943.
27. Hill, R. G.: United States Department of Agriculture, Misc. Publ. No. 167, 1933, Revised, 1941.
28. Jules S. Chernick, Junior Assistant in Marketing, State of New York, Dept. of Agriculture and Markets: Personal Communication.
29. Pearson, H. E.: Personal Communication.
30. Hermes, W. B.: J. Econom. Entomol. 21: 720, 1928.
31. Van Aelstyn, E. L., Health Officer, Price, Utah: Personal Communication.
32. Ward, R., Melnick, J. L., Horstmann, D. M.: Science 101: 491, 1945.

RESISTANCE OF COTTON RATS TO THE VIRUS OF POLIOMYELITIS

As Affected By Intake of Vitamin A, Partial Inanition and Sex

H. M. Weaver
Detroit, Mich.
With the Technical Assistance of Rose Fucinari and Norma Hastings

A NUMBER of clinical[1] and of experimental[2] studies have indicated that partial inanition and/or vitamin intake might influence susceptibility to the virus of poliomyelitis. Our own experience[3] has been that neither sex, partial inanition, nor the avitaminoses B and D significantly affect the susceptibility of cotton rats to the Armstrong-Lansing strain of the virus.

Since the virus of poliomyelitis undoubtedly enters the host through one or more epithelial surfaces, and since the physiologic state of epithelia is, among other factors, dependent upon an adequate intake of vitamin A,[4] it was thought advisable to study the possible effects of avitaminosis-A on the susceptibility of the host to the virus.

The present communication records the results of a number of experiments which were designed to test the effects of Vitamin A-free diets, of partial inanition and of sex on the susceptibility and on certain immunologic responses of cotton rats to the Armstrong-Lansing strain of the virus of poliomyelitis.

MATERIALS

The Armstrong-Lansing strain of the poliomyelitis virus which has been adapted to the cotton rat was employed in these studies. Unfiltered, lightly centrifuged stock suspensions of the virus were prepared exclusively from the brain stems and spinal cords of paralyzed cotton rats. These nervous tissues had been stored in buffered glycerine at 5° C. for a period of time not exceeding two months. During the course of this investigation, samples of the stock virus suspensions were injected in large quantities (intracerebrally, intranasally, intraperitoneally, and subcutaneously) into albino rats, wild rats, guinea pigs, Syrian hamsters, Swiss mice, and *Macacus rhesus* monkeys. We were unable to reproduce the disease in albino rats, wild rats, and guinea pigs. On the other hand, the disease was consistently reproduced by intracerebral inoculations of the virus into Swiss mice and *Macacus rhesus* monkeys. Suspensions of the spinal cords of the mice and of the monkeys repeatedly produced paralytic anterior poliomyelitis when injected intracerebrally into cotton rats. On three occasions a condition resembling anterior poliomyelitis developed in hamsters which had been inoculated with the virus. Although flaccid paralysis was observed in the animals, and microscopic sections of their spinal cords showed poliomyelitic lesions, we were unable to serially pass the virus beyond the second generation.

From the Department of Anatomy, Wayne University College of Medicine.
Aided by a grant from the National Foundation for Infantile Paralysis, Inc.

The cotton rats employed in this study were obtained from the Michigan Department of Health Laboratories.

The basic diet of the control animals was composed of a mixture of natural foods as follows: cane molasses, peanut oil meal, soy bean oil meal, animal liver meal, fish meal, meat scraps, condensed buttermilk, corn gluten, wheat bran, wheat flour middlings, ground whole oats, ground whole yellow corn, ground hulled barley, ground whole wheat, whole milk powder, alfalfa leaf meal, A and D feeding oil (a Rockland Farms product), steamed bone meal, salt, and precipitated chalk.

The vitamin A-free diet used in these experiments consisted of the following substances: wheat starch, 3,300 Gm.; casein (vitamin-free), 900 Gm.; Crisco, 500 Gm.; U.S.P. salt mixture No. 2, 200 Gm.; agar, 100 Gm.; yeast (type 180, Fleischmann), 140 Gm.; and yeast (type 2019, Fleischmann), 60 Gm.

EXPERIMENTAL PROCEDURE

The rats were weaned at 25 days of age and divided into two groups according to sex. The animals of each of the two groups were fed the basic diet ad libitum until they were 35 days of age. At this time one-half of the cotton rats in each of these groups were fed the vitamin A-free diet. The other one-half of the animals in each of these groups continued to receive the basic diet. Thus, the animals were divided into four groups of approximately equal numbers of vitamin A-deficient males, control males, vitamin A-deficient females, and control females. It was felt that this grouping would demonstrate differential susceptibility and immunologic response dependent on sex or upon nutrition.

The control animals which were fed the basic diet ad libitum thrived, presented no consistent abnormalities, and exhibited no particular susceptibility to intercurrent infections. Each of the control rats ate approximately 10 Gm. of the basic diet daily. On the other hand, the cotton rats which were fed the vitamin A-free diet ad libitum grew less, showed grossly a diminished deposition of fat, and exhibited increased susceptibility to intercurrent infections. Each of these rats consumed approximately 6 Gm. of the vitamin A-free diet daily.

When each animal attained the age of 8 weeks, the virus of poliomyelitis was administered by one of several experimental methods. In two experiments the virus was injected into the brain; in five it was injected or instilled into certain parts of the alimentary tract; in two it was instilled into certain parts of the respiratory tract; and in the three remaining experiments it was administered through certain unusual portals. In order to prevent death resulting from vitamin A deficiency, each vitamin A-deficient rat was returned to the basic diet two weeks after it had been inoculated with the virus.

Each animal was observed morning and evening for twenty-five days after administration of the virus. Any animal remaining free of symptoms during this interval of time was subjected to a three-way inoculation (0.1 c.c. given intracerebrally, 0.5 c.c. subcutaneously in the back and 0.06 c.c. intranasally) with a 10 per cent suspension of the virus. Cotton rats remaining free of symptoms for another twenty-five days were subjected to a second three-way reinoculation with the virus. Any animal failing to show symptoms of poliomyelitis after

the first (or original) inoculation and two three-way reinoculations with the virus was considered immune.

Each cotton rat said to have contracted poliomyelitis after its first inoculation with the virus, when the latter was administered by any route other than the intracerebral, satisfied the following four requirements: (1) Flaccid paralysis developed within twenty-five days after the virus was first administered, and observations of the animal at frequent intervals showed progressive paralysis. (2) Samples of the central nervous system showed histologic changes characteristic of anterior poliomyelitis. (3) The remaining portions of the central nervous system of the paralyzed cotton rat, when made up into a 10 per cent saline suspension and injected intracerebrally into three previously untreated cotton rats, reproduced symptoms of the disease in at least one of the three animals. (4) At least one of the three passage animals showed histologic changes in its central nervous system which are characteristic of anterior poliomyelitis.

All animals which contracted poliomyelitis were permitted to live twenty-four hours after paralysis was first observed. At the end of this period the extent of paralysis was recorded and the animal killed. The relative susceptibility of the cotton rats which contracted poliomyelitis after inoculation with the virus was judged from the number of extremities paralyzed and from the length of the incubation period (defined here as the number of days between the time of inoculation with the virus and the time the rat died or was killed). Any cotton rat in which paralysis developed in two or more extremities within fifteen days of an inoculation was considered to have no unusual resistance to the antigen.

RESULTS

Part 1. Comparative Susceptibility of Vitamin A-Deficient and Control Rats Subjected to Three-Way Inoculations and to Single Intracerebral Inoculations of the Virus.—

Experiment 1: In order to test the relative susceptibility of these experimental animals to three-way inoculations, each cotton rat was subjected to a three-way inoculation (0.1 c.c. intracerebral, 0.06 c.c. intranasal, and 0.5 c.c. subcutaneous in the back) with a 10 per cent suspension of the virus. Each of the animals in this group contracted the disease. Table I summarizes the results of this experiment.

TABLE I

ANIMALS	AVERAGE INCUBATION PERIOD (DAYS)†	EXTENT OF OBSERVABLE PARALYSIS (EXTREMITIES)
A-deficient rats* (34)	4.06 (2-8)	3.71 (2-4)
Control rats (32)	4.59 (2-8)	3.63 (2-4)
Males (34)	3.97 (2-7)	3.65 (2-4)
Females (32)	4.69 (2-8)	3.69 (2-4)
A-deficient males (18)	3.72 (2-7)	3.67 (2-4)
Control males (16)	4.25 (2-6)	3.63 (2-4)
A-deficient females (16)	4.44 (2-8)	3.75 (2-4)
Control females (16)	4.94 (2-8)	3.63 (2-4)

*Numbers in parentheses indicate number of animals.

†Defined here as the number of days between the time of inoculation with the virus and the time the rat died or was sacrificed.

Experiment 2: In order to test the relative susceptibility of these animals to intracerebral inoculation, each cotton rat was subjected to a single intracerebral inoculation with a 0.05 c.c. of a 1 per cent suspension of the virus. Every animal in this group contracted the disease. Table II summarizes the results of the experiment.

TABLE II

ANIMALS	AVERAGE INCUBATION PERIOD (DAYS)†	EXTENT OF OBSERVABLE PARALYSIS (EXTREMITIES)
A-deficient rats* (40)	5.00 (2-9)	3.10 (2-4)
Control rats (40)	4.18 (2-9)	3.15 (2-4)
Males (40)	4.65 (2-8)	3.20 (2-4)
Females (40)	4.53 (2-9)	3.05 (2-4)
A-deficient males (20)	5.00 (2-8)	3.20 (2-4)
Control males (20)	4.25 (2-8)	3.20 (2-4)
A-deficient females (20)	5.00 (2-9)	3.00 (2-4)
Control females (20)	4.10 (2-9)	3.10 (2-4)

*Numbers in parentheses indicate number of animals.

†Defined here as the number of days between the time of inoculation with the virus and the time the rat died or was sacrificed.

Part 2: Comparative Susceptibility of Vitamin A-Deficient and Control Rats Subjected to Inoculations or Instillations of the Virus Into Different Parts of the Alimentary Tract.—

Experiment 3: In order to test the relative susceptibility of these animals to food contaminated with the virus, each cotton rat devoured one brain stem and spinal cord which had been freshly removed from a cotton rat paralyzed with anterior poliomyelitis. To maintain the state of avitaminosis-A, brain stems and spinal cords fed to the vitamin A-deficient animals were in all cases removed from vitamin A-deficient cotton rats. Table III summarizes the results of this experiment.

TABLE III

ANIMALS	PARALYZED IN TWO OR MORE EXTREMITIES WITHIN USUAL INCUBATION PERIOD			RESISTANT TO TWO THREE-WAY REINOCULATIONS
	AFTER EXPERIMENTAL FEEDING	AFTER FIRST REINOCULATION	AFTER SECOND REINOCULATION	
A-deficient males (7)*	0	7	0	0
Control males (6)	0	6	0	0
A-deficient females (7)	0	7	0	0
Control females (6)	0	6	0	0

*Numbers in parentheses indicate number of animals.

Experiment 4: To test the relative susceptibility of cotton rats to virus administered through the upper pharynx, each rat received a single submucosal injection of 0.5 c.c. of a 10 per cent suspension of the virus into each of the two regions which in certain animals other than cotton rats house the palatine tonsils. Table IV summarizes the results of this experiment.

Experiment 5: This experiment was performed to test whether or not vitamin A deficiency might influence passage of viable virus through the upper gastrointestinal tract. Each cotton rat was subjected on each of three successive

TABLE IV

ANIMALS	PARALYZED IN TWO OR MORE EXTREMITIES WITHIN USUAL INCUBATION PERIOD			RESISTANT TO TWO THREE-WAY REINOCULATIONS
	AFTER EXPERIMENTAL INOCULATION	AFTER FIRST REINOCULATION	AFTER SECOND REINOCULATION	
A-deficient males (7)*	3	0	0	4
Control males (6)	0	0	0	6
A-deficient females (6)	2	0	0	4
Control females (7)	0	0	0	7

*Numbers in parentheses indicate number of animals.

days to a single intragastric instillation of 1.0 c.c. of a 10 per cent suspension of the virus administered by means of a stomach tube. Table V summarizes the results of this experiment.

TABLE V

ANIMALS	PARALYZED IN TWO OR MORE EXTREMITIES WITHIN USUAL INCUBATION PERIOD			RESISTANT TO TWO THREE-WAY REINOCULATIONS
	AFTER EXPERIMENTAL INSTILLATIONS	AFTER FIRST REINOCULATION	AFTER SECOND REINOCULATION	
A-deficient males (6)*	0	4	0	2
Control males (7)	0	7	0	0
A-deficient females (6)	0	3	0	3
Control females (7)	0	7	0	0

*Numbers in parentheses indicate number of animals.

Experiment 6: This experiment was performed to determine whether or not vitamin A deficiency might influence passage of viable virus through the lower gastrointestinal tract. Each cotton rat was subjected on each of three successive days to a single intracolonic instillation of 1.0 c.c. of a 10 per cent suspension of the virus administered by means of a rectal tube. Table VI summarizes the results of this experiment.

TABLE VI

ANIMALS	PARALYZED IN TWO OR MORE EXTREMITIES WITHIN USUAL INCUBATION PERIOD			RESISTANT TO TWO THREE-WAY INOCULATIONS
	AFTER EXPERIMENTAL INSTILLATIONS	AFTER FIRST REINOCULATION	AFTER SECOND REINOCULATION	
A-deficient males * (7)	2	0	0	5
Control males (6)	0	4	0	2
A-deficient females (7)	0	2	0	5
Control females (7)	0	5	0	2

*Numbers in parentheses indicate number of animals.

Experiment 7: In order to test the relative susceptibility of these animals to intraperitoneal inoculations, each cotton rat was subjected on each of three successive days to a single intraperitoneal inoculation with 1.0 c.c. of a 10 per cent suspension of the virus. Table VII summarizes the results of this experiment.

TABLE VII

ANIMALS	PARALYZED IN TWO OR MORE EXTREMITIES WITHIN USUAL INCUBATION PERIOD			RESISTANT TO TWO THREE-WAY INOCULATIONS
	AFTER EXPERIMENTAL INOCULATIONS	AFTER FIRST REINOCULATION	AFTER SECOND REINOCULATION	
A-deficient males* (7)	3	0	0	4
Control males (6)	0	0	0	6
A-deficient females (7)	1	0	0	6
Control females (7)	0	0	0	7

*Numbers in parentheses indicate number of animals.

Part 3. Comparative Susceptibility to Vitamin A-Deficient and Control Rats Subjected to Instillations of the Virus Into Different Parts of the Respiratory Tract.—

Experiment 8: To test whether or not vitamin A deficiency might alter susceptibility to virus entering through the upper respiratory tract, each cotton rat was subjected during the morning and again during the evening on each of three successive days to an intranasal instillation with the virus of poliomyelitis. On each of these occasions, 0.05 c.c. of a 10 per cent suspension of the virus was dropped into each nostril. Table VIII summarizes the results of this experiment.

TABLE VIII

ANIMALS	PARALYZED IN TWO OR MORE EXTREMITIES WITHIN USUAL INCUBATION PERIOD			RESISTANT TO TWO THREE-WAY INOCULATIONS
	AFTER EXPERIMENTAL INSTILLATIONS	AFTER FIRST REINOCULATION	AFTER SECOND REINOCULATION	
A-deficient males* (6)	0	6	0	0
Control males (7)	0	7	0	0
A-deficient females (7)	1	6	0	0
Control females (6)	0	6	0	0

*Numbers in parentheses indicate number of animals.

Experiment 9: To test the relative permeability of the pulmonary epithelium to the virus of poliomyelitis, each cotton rat was subjected to a single intrabronchial instillation of 0.1 c.c. of a 10 per cent suspension of virus by means of a tracheal catheter. Table IX summarizes the results of this experiment.

TABLE IX

ANIMALS	PARALYZED IN TWO OR MORE EXTREMITIES WITHIN USUAL INCUBATION PERIOD			RESISTANT TO TWO THREE-WAY INOCULATIONS
	AFTER EXPERIMENTAL INSTILLATIONS	AFTER FIRST REINOCULATION	AFTER SECOND REINOCULATION	
A-deficient males* (7)	0	7	0	0
Control males (6)	0	6	0	0
A-deficient females (7)	0	7	0	0
Control females (7)	0	7	0	0

*Numbers in parentheses indicate number of animals.

TABLE X

ANIMALS	PARALYZED IN TWO OR MORE EXTREMITIES WITHIN USUAL INCUBATION PERIOD			RESISTANT TO TWO THREE-WAY INOCULATIONS
	AFTER EXPERIMENTAL INOCULATIONS	AFTER FIRST REINOCULATION	AFTER SECOND REINOCULATION	
A-deficient males* (6)	1	0	0	5
Control males (7)	0	0	0	7
A-deficient females (7)	0	0	0	7
Control females (7)	0	1	0	6

*Numbers in parentheses indicate number of animals.

Part 4. Comparative Susceptibility of Vitamin A-Deficient and Control Rats Subjected to the Virus Administered by Unusual Methods.—

Experiment 10: This experiment was performed to determine whether or not vitamin A deficiency might influence susceptibility when the virus was introduced beneath the skin. Each cotton rat was subjected on each of three successive days to a single subcutaneous inoculation with a 1.0 c.c. of a 10 per cent suspension of the virus. Table X summarizes the results of this experiment.

Experiment 11: This experiment was performed to determine whether or not vitamin A deficiency might influence susceptibility when the virus was introduced into the blood stream by means of cardiac puncture. Each cotton rat was subjected to a single intracardiac inoculation of 0.5 c.c. of a 10 per cent suspension of the virus. Table XI summarizes the results of this experiment.

TABLE XI

ANIMALS	PARALYZED IN TWO OR MORE EXTREMITIES WITHIN USUAL INCUBATION PERIOD			RESISTANT TO TWO THREE-WAY INOCULATIONS
	AFTER EXPERIMENTAL INOCULATIONS	AFTER FIRST REINOCULATION	AFTER SECOND REINOCULATION	
A-deficient males* (6)	2	2	0	2
Control males (7)	0	0	0	7
A-deficient females (6)	0	0	0	6
Control females (6)	0	1	0	5

*Numbers in parentheses indicate number of animals.

Experiment 12: This experiment was performed to determine whether or not vitamin A deficiency might influence susceptibility following contact with a diseased animal. Each cotton rat was permitted to live in the same cage with

TABLE XII

ANIMALS	PARALYZED IN TWO OR MORE EXTREMITIES WITHIN USUAL INCUBATION PERIOD			RESISTANT TO TWO THREE-WAY INOCULATIONS
	AFTER EXPERIMENTAL CONTACT	AFTER FIRST REINOCULATION	AFTER SECOND REINOCULATION	
A-deficient males* (7)	0	7	0	0
Control males (6)	0	6	0	0
A-deficient females (6)	0	6	0	0
Control females (6)	0	6	0	0

*Numbers in parentheses indicate number of animals.

another cotton rat which had been subjected to a three-way inoculation with the virus. The experimental cotton rat remained in intimate contact with the inoculated animal until the latter became completely paralyzed. Table XII summarizes the results of this experiment.

COMMENT

It is conceivable that as a consequence of feeding vitamin A-deficient diets an altered susceptibility to paralytic anterior poliomyelitis might result because: (1) certain epithelia, which ordinarily would be impermeable to the virus, may be altered in such a manner that they would permit its passage; and/or (2) the "internal resistance" of the host (neutralizing substance, circulating virucidal substances, cellular resistance) may be less effective.

The results obtained in this study from experiments in which the virus was administered by intracerebral injections (Experiments 1 and 2), by feeding an infected brain stem and spinal cord (Experiment 3), by intrapulmonary instillations (Experiment 9) and by contact with an infected animal (Experiment 12), offered no evidence to indicate that susceptibility to the virus of poliomyelitis is related to vitamin A-deficient diets, to partial inanition or to sex. Whereas none of the animals in Experiments 3, 9, and 12 acquired the disease following their first exposure to the virus, it is interesting to note that all of these animals contracted the disease following three-way inoculations which were administered twenty-five days after their first exposure to the virus. Since none of these animals exhibited any unusual resistance to three-way inoculations, these results would indicate that during their first exposure little or no active virus entered the body through the epithelial membranes of the alimentary and respiratory tracts or the skin.

In contrast to these findings, the results of experiments in which the virus was administered by intratonsillar injections (Experiment 4); by intracolonic instillations (Experiment 6); by intraperitoneal injections (Experiment 7); by intranasal instillations (Experiment 8); by subcutaneous injections (Experiment 10) and by intracardiac injections (Experiment 11); indicate that cotton rats fed vitamin A-deficient diets are more susceptible to the virus of poliomyelitis than are rats which have been fed an adequate diet.

Whereas none of the animals which were given the virus by stomach tube (Experiment 5), and only two of the animals administered the virus by intracolonic instillation (Experiment 6), acquired the disease, a considerable number of the vitamin A-deficient rats in both of these experiments exhibited complete resistance to three-way inoculations which were administered twenty-five days after the rat was first exposed to the virus. These results seem to indicate that during their first exposure enough of the virus leaked through the epithelium of the alimentary tract to produce an acquired immunity to the disease.

The experiments reported in this communication do not indicate what effect partial inanition (each of the vitamin A-deficient rats consumed only about 60 per cent as much food as did the controls) might have on the susceptibility of cotton rats to the virus of poliomyelitis. In this regard, findings of previous

studies on vitamin B and D deficiencies[3] (during these experiments the deficient animals also suffered from partial inanition) are of importance. In this series no evidence was found that partial inanition, per se or in conjunction with vitamins B and D deficiencies, significantly influenced the susceptibility of cotton rats to the virus of poliomyelitis. If partial inanition plays any part in lowering the resistance of vitamin A-deficient cotton rats to the virus of poliomyelitis, it must be of minor importance.

It is commonly recognized that the male is more susceptible to the paralytic form of anterior poliomyelitis than is the female.[5] It is interesting to note that in the present investigation, of the fifteen vitamin A-deficient rats which contracted the paralytic form of the disease after the virus was administered by methods other than by intracerebral injection, only two were females. However, it would appear that the increased susceptibility evidenced by the males is not due primarily to sex because: (1) previous studies[3] showed no difference in susceptibility which could be attributed to sex, and (2) in the present investigation, the differences in susceptibility which could be related to sex were apparent only among the vitamin A-deficient animals.

Considerable caution should be exercised in applying to the human being our findings that vitamin A-deficient diet increases the susceptibility of cotton rats to the virus of poliomyelitis. Whereas the pathologic consequences of avitaminosis-A are similar in both species,[4] it is questionable whether the human being ever suffers from this type of malnutrition to the degree experienced by our animals.

SUMMARY AND CONCLUSIONS

This communication records the results of twelve experiments which were designed to test the effects of vitamin A-deficient diets, of partial inanition, and of sex on the susceptibility and on certain immunologic responses of cotton rats to the virus of poliomyelitis.

Suspensions of the Armstrong-Lansing strain of the virus of poliomyelitis were injected or instilled in varying quantities into the cerebrum, stomach, colon, peritoneal cavity, external nares, and blood stream, beneath the skin of the back and beneath the pharyngeal mucosa. In addition, the animals of one experimental group were allowed to remain in intimate contact with cotton rats succumbing to the effects of intracerebral inoculations with the virus. Finally, each cotton rat of still another experimental group was fed the brain stem and spinal cord freshly removed from a cotton rat paralyzed with poliomyelitis.

Each of the cotton rats which failed to develop paralysis after an experimental inoculation with the virus was subjected to three-way reinoculations with the virus at intervals of twenty-five days.

The results of these experiments yield no evidence to indicate that vitamin A-deficient diets affect the susceptibility or the resistance of cotton rats to the virus of poliomyelitis when the latter is administered by injections into the cerebrum, by instillations into the bronchi, by feeding an infected brain stem and spinal cord, or by contact with an infected cotton rat.

Evidence was presented to indicate that cotton rats fed vitamin A-deficient diets are more susceptible to the virus of poliomyelitis than are controls when the virus is administered by intratonsillar injections, by intracolonic instillations, by intraperitoneal injections, by intranasal instillations, by subcutaneous injections and by intracardiac injections.

Some evidence was presented to indicate that, in cotton rats fed vitamin A-deficient diets, the mucosa of certain parts of the alimentary tract may become more permeable to the virus of poliomyelitis than is the case among the controls.

It would appear that sex and partial inanition, suffered by all vitamin A-deficient rats, played no primary part in the results obtained in this study.

REFERENCES

1. (a) Broekema, H.: Maandschr. v. kindergeneesk. **8:** 193, 1939.
   (b) Giamondi, A.: Pediatria **48:** 48, 1940.
   (c) Hamburger, F.: Wien. klin. Wchnschr. **51:** 825, 1938.
   (d) Heaslip, W. G.: Australian J. Exper. Biol. & Sc. **16:** 287, 1938.
   (e) Helms, K.: M. J. Australia **1:** 717, 1941.
   (f) Huffman, O. V.: Lancet-Clinic **105:** 310, 1911.
   (g) Mathews, A. P.: Vitamins, Minerals and Hormones, Baltimore, 1937, William Wood & Company, 1937.
   (h) McCormick, W. J.: Canad. M. A. J. **38:** 261, 1938.
   (i) McCormick, W. J.: M. Rec. **150:** 302, 1939.
   (j) McCormick, W. J.: M. Rec. **155:** 89, 1942.
   (k) McCormick, W. J.: M. Rec. **155:** 525, 1942.
   (l) Stern, E. L.: Am. J. Clin. Med. **45:** 108, 1938.
   (m) Stone, S.: J. PEDIAT. **22:** 142, 1943.
2. (a) Foster, C., Jones, J. H., Henle, W., and Dorfman, F.: Proc. Soc. Exper. Biol. & Med. **51:** 215, 1942.
   (b) Foster, C., Jones, J. H., Henle, W., and Dorfman, F.: Science **97:** 207, 1943.
   (c) Jungeblut, C. W.: J. Exper. Med. **65:** 127, 1937.
   (d) Jungeblut, C. W.: J. Exper. Med. **66:** 459, 1937.
   (e) Jungeblut, C. W.: J. Exper. Med. **70:** 315, 1939.
   (f) Lichstein, H. C., Waisman, H. A., Elvehjem, C. A., and Clark, P. F.: Proc. Soc. Exper. Biol. & Med. **56:** 3, 1944.
   (g) Rasmussen, A. F., Waisman, H. A., Elvehjem, C. A., and Clark, P. F.: J. Infect. Dis. **74:** 41, 1944.
   (h) Sabin, A. B.: J. Exper. Med. **69:** 507, 1939.
   (i) Sabin, A. B., Ward, R., Rapoport, S., and Guest, G. M.: Proc. Soc. Exper. Biol. & Med. **48:** 451, 1941.
   (j) Toomey, J. A.: Am. J. Dis. Child. **53:** 1202, 1937.
   (k) Toomey, J. A.: Am. J. Dis. Child. **53:** 1490, 1937.
   (l) Toomey, J. A., and Takacs, W. S.: Am. J. Dis. Child. **56:** 1274, 1938.
   (m) Toomey, J. A., and Takacs, W. S.: J. Bact. **39:** 64, 1940.
   (n) Toomey, J. A., Frohring, W. D., and Takacs, W. S.: Yale J. Biol. & Med. **16:** 477, 1944.
   (o) Waisman, H. A., Rasmussen, A. F., Elvehjem, C. A, and Clark, P. F.: J. Nutrition **26:** 205, 1943.
3. (a) Weaver, H. M.: J. PEDIAT. **24:** 88, 1944.
   (b) Weaver, H. M.: Am. J. Dis. Child. **69:** 26, 1945.
4. Wolbach, S. B.: J. A. M. A. **108:** 7, 1937.
5. International Committee for the Study of Infantile Paralysis: Poliomyelitis; A Survey. . . . , Baltimore, 1932, Williams and Wilkins Company.

THE USE OF SULFAMERAZINE IN INFANTS AND CHILDREN

GILBERT B. FORBES, M.D., ANNE PERLEY, M.A., AND JEAN DEHLINGER, M.D.
ST. LOUIS, MO.

SULFAMERAZINE* (2-sulfanilamido-4-methylpyrimidine), the monomethyl derivative of sulfadiazine,[1] is in fairly wide clinical use at the present time, and certain advantages have been claimed for it over the other commonly employed sulfonamide drugs, particularly sulfadiazine: (1) Sulfamerazine is more quickly and completely absorbed from the gastrointestinal tract[2, 3] and therefore may be satisfactorily administered orally in many instances in which parenteral administration would be more desirable if certain of the other sulfonamide drugs were used. (2) Sulfamerazine is excreted much more slowly by the kidney than either sulfadiazine or sulfathiazole[3, 4] and for this reason may be administered at less frequent intervals and in smaller amounts with the attainment of comparable levels in the blood. (3) The therapeutic value of sulfamerazine has proved to be equal to that of sulfadiazine and sulfathiazole both in the treatment of infections in human beings and in experimental infections in animals.[5-8] (4) The toxic effects of sulfamerazine are certainly no greater and possibly somewhat less than those of sulfadiazine and sulfathiazole.[2, 5, 6, 9]

Since the methods of administration of the various sulfonamide drugs to adults cannot be applied satisfactorily to the treatment of infants and children and since the toxic effects in infants and children and in adults may vary considerably, we have undertaken a study of the use of sulfamerazine in patients in the pediatric age group for the primary purpose of establishing a rational dosage scheme for both oral and parenteral administration of the drug. As the work continued, it seemed desirable to include observations on the distribution of sulfamerazine in the various body fluids, on the toxic effects of the drug, and in a limited way on its therapeutic usefulness. The study embraced the period from December, 1943, through June, 1944, during which time 135 unselected hospitalized infants and children with various types of infections were treated with sulfamerazine.

THE ABSORPTION OF SULFAMERAZINE FROM THE GASTROINTESTINAL TRACT

Single oral doses of sulfamerazine of 0.1 Gm. per kilogram body weight were given to a number of children,† and the level of free sulfamerazine‡ in the blood was determined at intervals during the succeeding twenty-four hours. The results are shown in Fig. 1 in which the subjects are divided into two groups, those two years of age or older and those in the first or second year of life. It is evident from the average values indicated at the top of each portion of the chart

From the Department of Pediatrics, Washington University School of Medicine, and the St. Louis Children's Hospital.

*A portion of the sulfamerazine used in this study was provided through the courtesy of the Medical Research Division of Sharp & Dohme, Inc.

†Patients with known renal or enteric disease were carefully excluded from this portion of the study.

‡The analyses for sulfamerazine in the blood and other body fluids were made by the method of Bratton and Marshall,[10] adapted for a sample of 0.1 c.c. Unless otherwise indicated, all values for sulfamerazine in this paper are for the free form of the drug.

that the absorption of the drug is somewhat better in the older age group. The average blood concentration is seen to increase until the eighth hour following administration and then to fall very gradually, so that there is still an appreciable concentration at the end of twenty-four hours. It may be concluded that sulfamerazine is absorbed rapidly from the gastrointestinal tract and is excreted rather slowly. There is, however, considerable individual variation in the rate of both absorption and excretion.

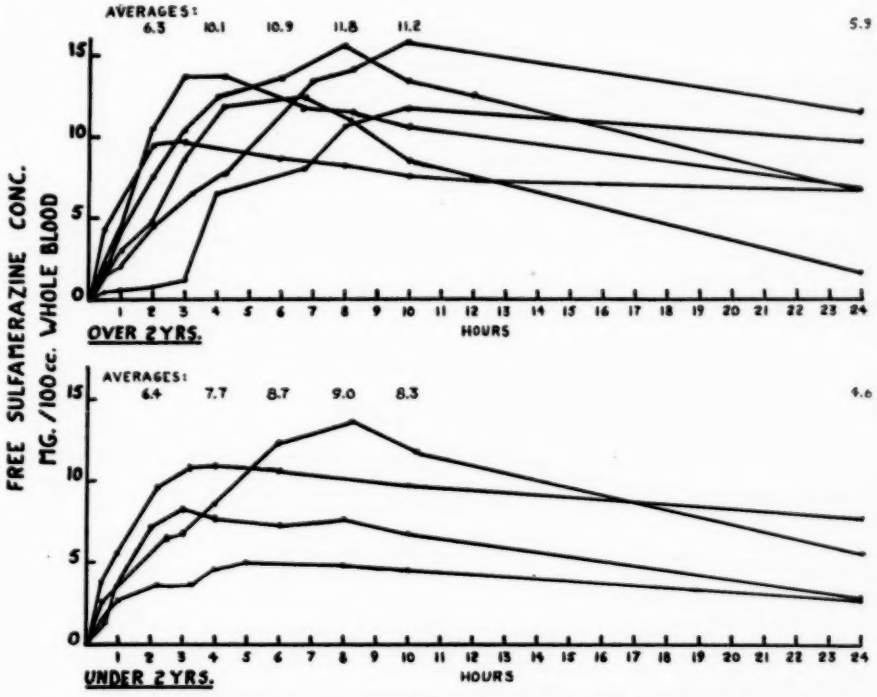


Fig. 1.—Blood concentrations of free sulfamerazine following single oral doses of 0.1 Gm. of sulfamerazine per kilogram body weight to children 2 years of age and older and to infants.

Since sulfamerazine is so readily absorbed from the gastrointestinal tract, an attempt was made to attain very high blood concentrations of the drug in young infants through oral administration alone. Fig. 2 illustrates the results of giving a single oral dose of 0.4 Gm. per kilogram of body weight. The average blood values are seen to be somewhat greater than those in the infants who received 0.1 Gm. per kilogram of body weight, but the differences are not marked. The larger dose resulted in about the same blood level at two hours as did the smaller; in one case the level finally reached 21.4 mg. per cent, but only after twenty-four hours. It is apparent, as in the case of the other sulfonamide drugs, that infants are not able to absorb rapidly from the gastrointestinal tract very large amounts of sulfamerazine. In time, high concentrations could

doubtless be achieved in this manner, but usually in critically ill patients it is desirable to obtain the high blood levels quickly.

The matter of proper maintenance dosage of the drug for sick infants and children was considered, and the following dosage scheme was decided upon: an initial dose of 0.1 Gm. of sulfamerazine per kilogram body weight to be followed by 0.05 Gm. per kilogram body weight at eight-hour intervals. The total daily dosage then amounts to 0.15 Gm. per kilogram body weight or three-

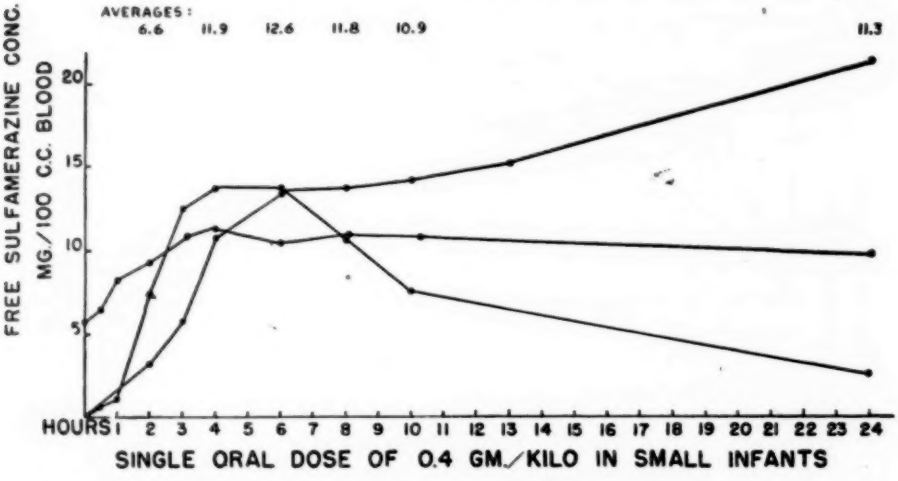


Fig. 2.—Blood concentrations of free sulfamerazine following single oral doses of 0.4 Gm. of sulfamerazine per kilogram body weight to infants in the first year of life.

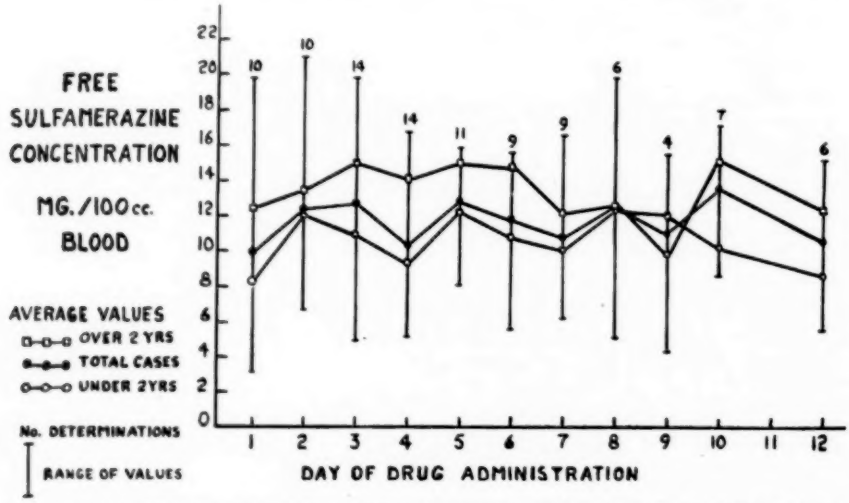


Fig. 3.—Blood concentrations of free sulfamerazine produced by the repeated oral administration of 0.05 Gm. of sulfamerazine per kilogram body weight every 8 hours to children of various ages, following an initial dose of 0.1 Gm. per kilogram body weight.

fourths of the dosage usually employed with the other sulfonamide drugs. In treating older children, a daily dose of 5.0 Gm. is not exceeded regardless of the patient's weight. It will be seen (Fig. 3) that in older children the average blood levels varied from 10 to 15 mg. per cent and in infants from 8 to 12 mg. per cent. Such levels are adequate in the treatment of patients with infections which are not unusually severe.

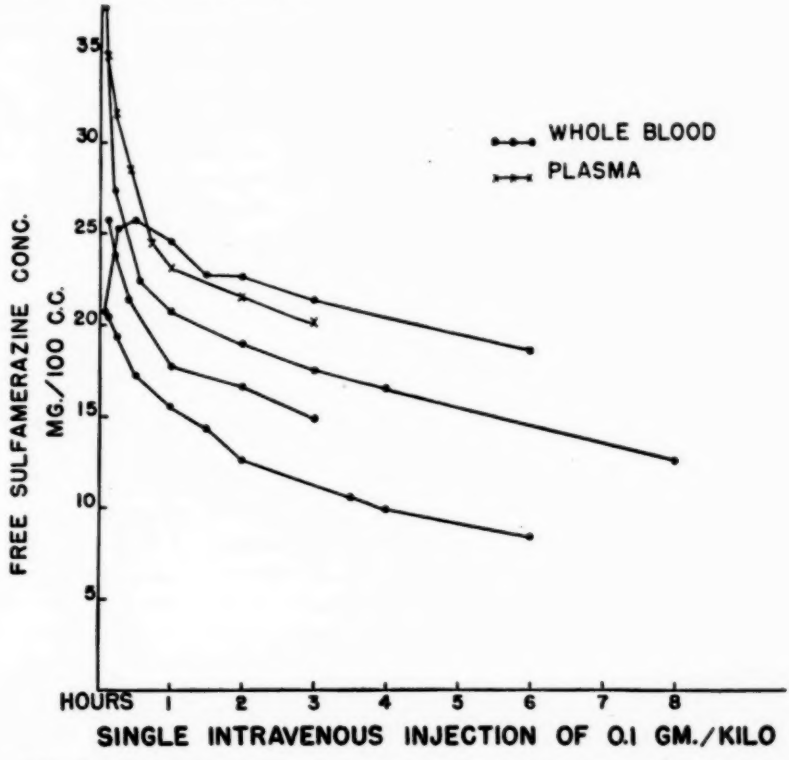


Fig. 4.—Blood concentrations of free sulfamerazine following a single intravenous injection of 0.1 Gm. of sodium sulfamerazine per kilogram body weight, made up as a 5 per cent solution in distilled water.

PARENTERAL ADMINISTRATION OF SODIUM SULFAMERAZINE

Intravenous Administration.—Fig. 4 illustrates the blood levels following a single intravenous injection of 0.1 Gm. of sodium sulfamerazine per kilogram body weight. The drug was prepared as a 5 per cent solution in distilled water. The concentration, after the high initial peak, dropped rapidly during the first hour following the injection and then decreased gradually. The blood levels were not followed for longer than eight hours since the rate of excretion after this period is largely independent of the mode of administration of the drug.

Subcutaneous Administration.—A special study was made of this method of administration since it seems to be preferable when any of the sulfonamide

drugs are to be given parenterally. Adequate blood levels may be attained promptly; the technique of administration is easy and, therefore, particularly desirable when the injection must be repeated many times; the injection can also provide water and alkali at the same time that the drug is being given; the initial undesirably high blood concentration which occurs after intravenous injection is obviated. Fig. 5 illustrates the blood levels obtained with subcutaneous

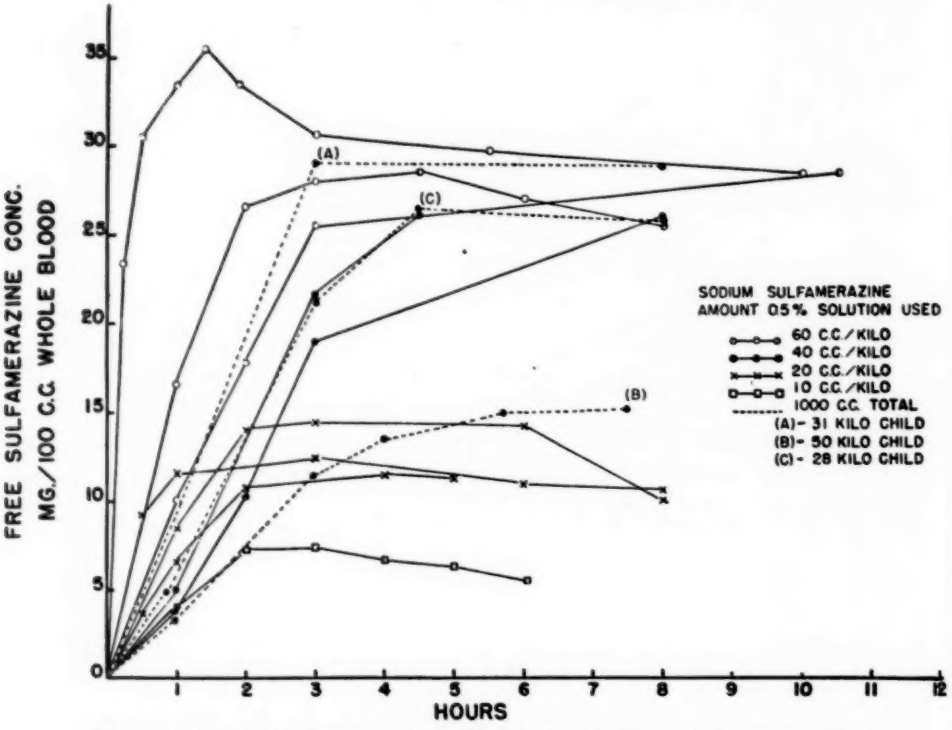


Fig. 5.—Blood concentrations of free sulfamerazine following single subcutaneous injections of varying amounts of 0.5 per cent sodium sulfamerazine in half "fortified lactate Ringer's" solution.

administration of varying amounts of 0.5 per cent sodium sulfamerazine. The drug was made up in either plain or half "fortified lactate Ringer's"* solution and administered as an ordinary hypodermoclysis. No local reaction was observed even when concentrations of 1 per cent were used, and pain seemed to be no greater than that occurring with other hypodermoclyses.

As the amount of solution given is increased from 10 c.c. per kilogram body weight to 60 c.c. per kilogram (i.e., 0.05 Gm. to 0.3 Gm. of drug per kilogram), the rate of absorption is seen to be more rapid and the blood level attained in a

*Plain lactate Ringer's: A solution of 1/10 molar sodium-r-lactate in slightly hypotonic Ringer's.

Half "fortified lactate Ringer's": A mixture of three parts by volume of 1/6 molar sodium-r-lactate and four parts of Ringer's solution.

given period of time higher. Ten cubic centimeters of 0.5 per cent solution per kilogram does not produce an adequate blood level, whereas 20 c.c. (0.1 Gm.) per kilogram results in a level about equal to that produced by the same amount of drug given orally. The 40 c.c. and 60 c.c. per kilogram doses produce a high blood level with a rapidity which is quite adequate in patients with severe infections. The uppermost curve was obtained on a very dehydrated child; the speed of absorption here was amazing, the blood level reaching 23.4 mg. per cent within fifteen minutes.

The curves marked (*A*), (*B*), and (*C*) represent cases in which 1,000 c.c. of 0.5 per cent solution of sodium sulfamerazine was given to children of various weights. This amount seems adequate for most larger children, and we have not found it necessary to give single doses of more than 5.0 Gm. of drug to a child by this route regardless of body weight. In adults, the administration of 5.0 Gm. of sodium sulfamerazine subcutaneously every eight hours has resulted in blood levels of between 20 and 30 mg. per cent.[11]

THE ADMINISTRATION OF SULFAMERAZINE TO PATIENTS WITH SEVERE INFECTIONS

On the basis of these observations we attempted to work out a rational scheme for rapidly attaining blood concentrations of 25 to 30 mg. per cent and maintaining such levels until the patient's infection is definitely subsiding. Fig. 6 illustrates the scheme in the treatment of a disease such as meningococcic meningitis; that is, one which is severe yet responds rapidly to sulfonamide therapy. For the first two days the drug is given subcutaneously, the initial dose being 60 c.c. of a 0.5 per cent solution per kilogram body weight. Subsequent doses of 20 c.c. per kilogram are given at eight-hour intervals. The blood concentration usually reaches 25 mg. per cent within two hours after the beginning of treatment and is maintained, on the average, near 30 mg. per cent for the next two days. At the end of this time the patient is often able to take oral medication, the very high blood level is no longer as essential, and thereafter sulfamerazine is administered orally in doses of 0.1 Gm. per kilogram every eight hours. The average blood level then usually drops to between 15 and 20 mg. per cent where it is maintained until the infection is well under control. Subsequent therapy consists of giving the patient 0.05 Gm. per kilogram every eight hours. In Fig. 6 are shown the values obtained in five patients, all suffering from acute purulent meningitis, the average blood concentrations being indicated by the clear line in the center of the black area.

In cases of meningitis due to the pneumococcus, hemolytic streptococcus, or the influenzal bacillus, in which high drug levels should be maintained for longer periods of time, subcutaneous sodium sulfamerazine may be continued as long as necessary. With careful following of the blood concentrations of sulfamerazine, the dosage may be adjusted to produce suitable levels. With the ease of subcutaneous administration of the drug and the absence of local irritation from the injection, we have been able to administer sodium sulfamerazine to several patients by the subcutaneous route alone for as long as three weeks without untoward effects.

It is essential, however, that daily blood determinations of the drug should be made when subcutaneous administration is being employed in such dosages. While Fig. 6 indicates that the average blood concentrations attained were satisfactory when the described schemes were used, it also illustrates that considerable variation may occur. For example, at the end of the second day, the spread exhibited by the five patients was from 20.8 mg. per cent to 40.8

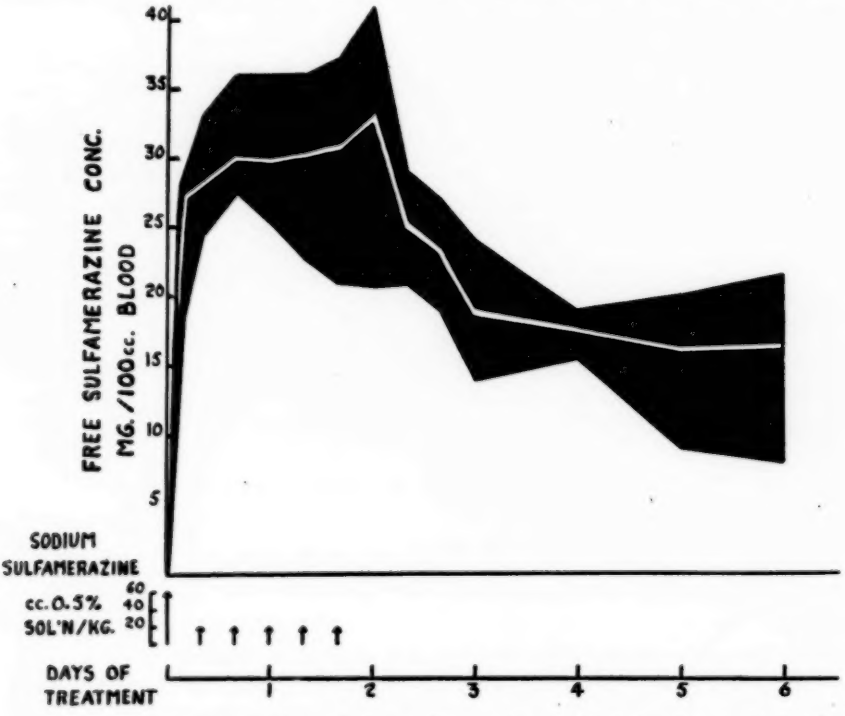


Fig. 6.—Blood concentrations of free sulfamerazine produced by the repeated subcutaneous administration of 0.5 per cent sodium sulfamerazine at eight-hour intervals, followed by oral doses of 0.1 Gm. of sulfamerazine per kilogram body weight given every eight hours.

mg. per cent despite the fact that they were given identical doses of sulfamerazine on the basis of body weight. In general, in any given patient, one can predict more closely the blood concentration when the drug is administered orally in ordinary dosages (0.15 Gm. per kilogram per day) than when higher dosages are employed. Finally, it should be remembered that parenteral administration of sulfamerazine is essential for the attainment of very high blood concentrations, particularly in small infants.

THE DISTRIBUTION OF SULFAMERAZINE IN THE VARIOUS BODY FLUIDS

It has been reported that sulfamerazine passes into the cerebrospinal fluid to the extent of about 50 per cent of the concentration in whole blood.[5, 6] This

value is in keeping with the relatively high degree of binding of the drug by plasma proteins.[4, 12] However, in the reported observations, no indication is given of the variation in the concentration of the drug in the blood during the several hours preceding the withdrawal of blood and spinal fluid for analysis. Although changes in the blood level are reflected in the spinal fluid, the change in spinal fluid concentration may lag considerably. This phenomenon probably accounts for the considerable variation in the ratio of spinal fluid to blood concentration which is so often noted in clinical practice and also for the fact that occasionally the concentration in the spinal fluid may actually exceed that in the blood in isolated samplings. With this in mind, we attempted to determine the ratios of the drug concentration in various body fluids to that in whole blood and plasma on occasions when it was known that the blood concentration had not changed markedly during the four-hour period prior to obtaining the blood and other body fluid specimens on which these ratios were calculated.

The data obtained are shown in Table I which includes observations on spinal fluid, pleural fluid, and ascitic fluid. The studies involving spinal fluid were all performed on patients suffering from either purulent or tuberculous meningitis, and those on pleural and ascitic fluid on a patient in the nephrotic stage of chronic glomerulonephritis who had a plasma albumin concentration of only 1.1 Gm. per cent. Metycaine* was used as a local anesthetic prior to withdrawal of all fluids for sulfamerazine analysis.

TABLE I. DISTRIBUTION OF SULFAMERAZINE IN VARIOUS BODY FLUIDS

CASE	DATE	DAY OF DRUG THERAPY	VARIATION IN BLOOD LEVEL DURING PRECEDING 4 HOURS (%)	WHOLE BLOOD (MG. %)	PLASMA (MG. %)	SPINAL FLUID (MG. %)	RATIOS: SPINAL FLUID WHOLE BLOOD (%)	RATIOS: SPINAL FLUID PLASMA (%)
E. W.	3/ 9/44	3	10.6	34.7	40.3	28.9	83.3	71.7
J. B.	3/18/44	3	7.1	34.0	35.9	20.8	61.2	58.0
J. H.	5/ 1/44	3	8.3	27.4	32.3	20.3	74.1	62.8
J. M.	5/ 7/44	7	12.9	38.4	43.6	25.5	66.4	58.2
D. K.	5/11/44	7	14.5	41.7	44.2	32.1	76.9	72.6
D. K.	5/16/44	12	3.5	13.8	18.6	8.7	63.0	46.7
B. E.	5/11/44	13	1.1	17.0	21.0	8.7	51.3	41.4
Average							68.0	58.9

CASE	DATE	DAY OF DRUG THERAPY	VARIATION IN BLOOD LEVEL DURING PRECEDING 4 HOURS (%)	WHOLE BLOOD (MG. %)	PLASMA (MG. %)	PLEURAL FLUID (MG. %)	PLEURAL FLUID WHOLE BLOOD (%)	PLEURAL FLUID PLASMA (%)
D. D.	4/11/44	2	1.1	11.1	11.0	10.1	91.0	92.0
D. D.	4/12/44	3	2.0	10.8	11.4	11.4	105.0	100.0

CASE	DATE	DAY OF DRUG THERAPY	VARIATION IN BLOOD LEVEL DURING PRECEDING 4 HOURS (%)	WHOLE BLOOD (MG. %)	PLASMA (MG. %)	ASCITIC FLUID (MG. %)	ASCITIC FLUID WHOLE BLOOD (%)	ASCITIC FLUID PLASMA (%)
D. D.	4/11/44	2	1.1	11.1	11.0	10.6	95.5	96.5
D. D.	4/12/44	3	2.0	10.8	11.4	10.9	101.0	95.6

*Gamma-(2-methylpiperidino) propylbenzoate hydrochloride, Eli Lilly and Company.

The ratios of the drug concentration in spinal fluid to that in whole blood and in plasma averaged 68 per cent and 59 per cent, respectively, and do not differ greatly from those for sulfadiazine and sulfapyrazine but are distinctly higher than those for sulfathiazole.

The data on the concentration of sulfamerazine in ascitic and pleural fluid indicate that in the one patient we observed, the drug distributed itself approximately equally between those fluids and the blood plasma, a finding in agreement with the earlier observations of Hageman and his coworkers.[6] Murphy and his coworkers,[3] however, found a much lower rate to exist between pleural and ascitic fluid and blood serum. It is possible that the very low plasma albumin in the patient which we studied may have affected somewhat the degree of binding of the drug in the plasma and, therefore, may have influenced its distribution between the plasma and the fluids mentioned.

THE EFFECTIVENESS OF SULFAMERAZINE IN VARIOUS CLINICAL INFECTIONS

A total of 135 unselected infants and children with various infections were treated with sulfamerazine during the course of this study. The drug was administered in accordance with the plans we have outlined. High drug dosages were employed in those patients suffering from meningitis, peritonitis, and severe respiratory infections and the lower dosages in those with the less severe infections. In treating these patients an attempt was made to compare the course of the illness with that in patients treated in the past with other sulfonamide drugs.

Acute Meningitis.—Seventeen patients with acute meningococcic meningitis were treated with sulfamerazine; all of these recoverd. The response to treatment was prompt in each case and quite satisfactory from the standpoint of both clinical and laboratory findings.

Sulfamerazine was used in one case of pneumococcal meningitis and mastoiditis and one case of influenzal (type B) meningitis with satisfactory recoveries in both. One case of hemolytic streptococcal meningitis was treated with sulfamerazine; penicillin was also used, however, so the effectiveness of the sulfamerazine cannot be evaluated.

Sulfamerazine was administered in high dosage in one case of tuberculous meningitis. There was no observable effect on the course of the infection.

Acute Peritonitis.—Four cases were treated. Two of these were due to the colon bacillus. In one, the infection was primary; in the other a generalized peritonitis secondary to an acute appendicitis was present. There was recovery in both. One patient whose case was of pneumococcal origin died within twelve hours of the onset of therapy. The fourth patient, who also died, was a young infant who suffered from cirrhosis of the liver, the organism responsible for the peritonitis being the *Staphylococcus aureus.*

Infections of the Upper Respiratory Tract.—Six cases of acute streptococcal tonsillitis were treated, all of which exhibited prompt alleviation of symptoms. Two cases of acute laryngitis, due to the streptococcus, responded well to sulfamerazine, although in one of these a tracheotomy was necessary to relieve dyspnea. The response to treatment was quite striking in a one-year-old infant who had developed acute thyroiditis secondary to acute tonsillitis and laryngitis.

Infections of the Lower Respiratory Tract.—Ten cases of typical lobar pneumonia were treated with sulfamerazine, and prompt improvement occurred in each case. One case of pneumococcal empyema with bacteremia improved after the institution of surgical drainage and the use of sulfamerazine. Six patients with bronchopneumonia, all of them small infants, improved promptly with sulfamerazine therapy. Six cases of severe bronchitis did well under treatment with the drug.

Miscellaneous Infections.—Those cases in which an evaluation of the effectiveness of sulfamerazine seemed possible are as follows: two cases of erysipelas, one of acute colon bacillus pyelitis, one of cellulitis of the thigh with accompanying femoral adenitis, and two cases of exfoliative dermatitis of the newborn. In all of these, improvement with drug therapy was prompt and satisfactory. Aside from the case of staphylococcal peritonitis mentioned previously, there was only one case of severe staphylococcal infection in this series. The patient had a deep iliac adenitis and was given large doses of sulfamerazine for nine days during which time he remained toxemic and febrile; improvement did not begin until the area of suppuration was surgically drained.

The remaining cases included catarrhal and suppurative otitis media, a variety of upper respiratory infections, acute laryngotracheobronchitis, bronchiolitis, cervical adenitis, and certain other infections in which it was impossible to evaluate the effectiveness of sulfamerazine. On several occasions the drug was given prophylactically in connection with surgical procedures to patients with rheumatic fever and to patients with intussusception, strangulated hernias, and tracheobronchial foreign bodies, for the purpose of minimizing any complicating infection.

THE TOXIC EFFECTS OF SULFAMERAZINE

Each patient in this series was carefully observed for possible toxic reactions. Many of the infants and children were treated for periods of not longer than one week, so that those reactions which ordinarily occur late were rarely encountered. Sodium lactate was given to each patient either orally or parenterally in an attempt to render the urine alkaline. For this purpose, 5 c.c. of a one molar solution per kilogram body weight per twenty-four hours were given orally in either four or six divided doses.[11] For those patients receiving sulfamerazine subcutaneously, sodium lactate was incorporated into the subcutaneous infusion in a dosage of 30 c.c. of 1/6 molar solution per kilogram body weight per twenty-four hours. This quantity usually has been found sufficient to keep the urinary pH above 7.0. We prefer sodium lactate to sodium bicarbonate because it does not produce gastric distress, it is easily administered to small infants and can be incorporated readily into any subcutaneous or intravenous infusion fluid.

We have divided the patients into two groups with respect to the level of sulfamerazine attained in the blood, the dividing line being a concentration of 15 mg. per cent, and have listed in Table II the toxic reactions occurring in each group. One hundred and twelve of the patients had blood levels less than 15 mg. per cent. In the other twenty-three patients, because of the severity of their

TABLE II

TOXIC EFFECT	LOW BLOOD LEVEL GROUP (112 CASES)		HIGH BLOOD LEVEL GROUP (23 CASES)		TOTALS	
	NO.	%	NO.	%	NO.	%
Fever	4	3.6	1	4.4	5	3.7
Rash	4	3.6	0	0	4	3.0
Rash and fever	2	1.8	0	0	2	1.5
Leucopenia	0	0	4	17.4	4	3.0
Anemia	0	0	1	4.4	1	0.7
Anorexia	1	0.9	0	0	1	0.7
Vomiting	1	0.9	0	0	1	0.7
Transitory microscopic hematuria	9	8.0	3	13.0	12	8.9
Microscopic hematuria	13	11.6	4	17.4	17	12.6
Gross hematuria	2	1.8	0	0	2	1.5
Oliguria and albuminuria	0	0	1	4.4	1	0.7

infections, an effort was made to maintain the blood levels between 25 and 30 mg. per cent with an observed range of from 15 to 50 mg. per cent.

Drug fever and rash were of the same general character as those seen with sulfadiazine. The rash was macular and erythematous in character, of varied distribution, and disappeared promptly when the drug was discontinued.

Leucopenia (total white cell count below 4,000 c.mm.) developed gradually in each of the four cases listed. The percentage of polymorphonuclear cells did not drop below 18; in two instances the leucocyte count rose gradually to normal although the drug was continued, while in the other two the drug was stopped. In no instance could the reaction be called a true agranulocytosis. In the one patient in whom anemia was observed, the hemoglobin dropped to 9.5 Gm. per 100 c.c. The anemia was corrected by blood transfusion and did not recur despite the continuance of the drug.

In infants and children, anorexia and vomiting often occur in the presence of infections, and it was not possible to determine to what extent these effects might have been due to the drug. In only two patients were anorexia and vomiting thought to be due to the administration of sulfamerazine, and in general the drug was extremely well tolerated.

Whenever possible, daily urinalyses were done in an effort to detect and to determine the extent of any renal complication which might occur from sulfamerazine. As already mentioned, all of the patients were given sodium lactate in an attempt to keep the urine alkaline. Crystals of sulfamerazine, both the free and acetylated forms, were seen frequently in the urinary sediment, but no attempt was made to determine the frequency with which crystalluria occurred. Nine per cent of the total group exhibited mild transitory microscopic hematuria. Such microscopic hematuria is fairly common in sick infants and children, and it is impossible to say that this finding was due to the drug rather than to the infection for which the patient was being treated. Twelve and six-tenths per cent of the patients exhibited microscopic hematuria of such degree and duration as to be classed as a true renal reaction to sulfamerazine. The reaction occurred somewhat more often in those patients receiving large doses of drug rather than in those receiving smaller amounts. Whenever such hematuria oc-

curred, measures were instituted to increase the alkalinity and the volume of the urine with resultant clearing of the urine on each occasion.

Gross hematuria occurred only twice in this series, both of the patients being in the "low blood level" group. In one the urine was definitely alkaline to litmus and in the other acid. Hematuria subsided in each instance after withdrawal of the drug and the administration of fluids and sodium lactate. In one patient in the "high blood level" group definite oliguria developed, and the urine showed 1 plus albumin by the heat and acetic acid test but no other abnormalities. The albuminuria ceased, and adequate urine flow was quickly established when fluids were administered intravenously.

On no occasion in this series were any of the more serious renal complications such as anuria, renal colic, or toxic nephrosis noted.

Sulfamerazine was administered to six patients with nephritis for periods ranging from three to twenty-seven days for the purpose of treating complicating infections. In no instance could we detect evidence that the drug tended to accentuate the pathologic process in the kidney. It is important to remember in using the drug in patients with impairment of renal function that it may be necessary to reduce the dosage appreciably in order to avoid excessively high levels in the blood.

COMMENT

From this study it is evident that the principal advantages which sulfamerazine offers over the other commonly used sulfonamide drugs in treating infants and children are that satisfactory blood concentrations can be produced by a smaller total daily dosage of the drug and that the doses may be given at less frequent intervals. The hope that, because of rapid absorption of the drug from the gastrointestinal tract, the parenteral route for the administration of sulfamerazine to infants and children could be dispensed with in many instances has not materialized. Our data show clearly the need for parenteral administration when high blood concentrations are desired quickly, and we feel that the subcutaneous route is the one of choice.

As far as therapeutic effectiveness is concerned, it is apparent that this series of cases is not large enough to warrant a statistical comparison of the effectiveness of sulfamerazine with that of sulfapyrazine, sulfadiazine, and sulfathiazole. However, it is our definite impression that it is as valuable as are the others.

From the standpoint of toxicity in infants and children, sulfamerazine offers no advantage over sulfadiazine and appears to be somewhat more toxic than sulfapyrazine.[13] The reactions encountered in this series were mild, there being none which could be classed as serious. In view of the routine use of sodium lactate, it is surprising that microscopic hematuria occurred so frequently in this series. Gross hematuria occurred in only two patients and albuminuria and oliguria only once. Whether these renal complications would have occurred more often had alkali not been administered concurrently is difficult to say.

SUMMARY

A study of the absorption, methods of administration, therapeutic effectiveness, and toxicity of sulfamerazine in an unselected group of 135 infants and children with infections revealed the following pertinent data:

1. Sulfamerazine is rapidly absorbed from the gastrointestinal tract and rather slowly excreted by the kidney. Accordingly, adequate blood concentrations are easily attained by the oral administration of 0.05 Gm. per kilogram of body weight every eight hours (three-quarters of the total daily dosage usually employed with sulfathiazole and sulfadiazine). Sulfamerazine thus possesses an advantage over the other sulfonamide drugs in that they must be given in larger total dosage with more frequent doses to attain comparable blood levels.

2. High blood concentrations are easily and rapidly produced by the subcutaneous administration of sodium sulfamerazine. The absorption of sulfamerazine from the gastrointestinal tract, although more rapid and complete than is the absorption of the other sulfonamide drugs, does not lead to values sufficiently high to obviate the need for parenteral administration of the drug when very high values are desired.

3. Sulfamerazine was observed to pass into the spinal fluid to the extent of from 52 to 83 per cent of the whole blood value and 41 to 73 per cent of the plasma value, while the concentration in pleural and ascitic fluid equaled that in the plasma.

4. From a purely clinical evaluation, the therapeutic effectiveness of sulfamerazine is entirely comparable to that of sulfapyrazine, sulfadiazine and, sulfathiazole.

5. The toxic reactions encountered were relatively frequent but, for the most part, were mild, and no serious reactions occurred. On the basis of our past experience, the frequency of toxic reactions was definitely greater with the use of sulfamerazine than with sulfapyrazine and certainly as great as with sulfadiazine.

REFERENCES

1. Roblin, R. O., Williams, J. H., Winnek, P. S., and English, J. P.: J. Am. Chem. Soc. **62**: 2002, 1940.
2. Welch, A. D., Mattis, P. A., Latven, A. R., Benson, W. M., and Shields, E. H.: J. Pharmacol. & Exper. Therap. **77**: 357, 1943.
3. Murphy, F. D., Clark, J. K., and Flippin, H. F.: Am. J. Med. Sc. **205**: 717, 1943.
4. Earle, D. P., Jr.: J. Clin. Investigation **23**: 914, 1944.
5. Flippin, H. F., Reinhold, J. G., and Gefter, W. I.: M. Clin. North America **27**: 1447, 1943.
6. Hageman, P. O., Harford, C. G., Sobin, S. S., and Ahrens, R. E.: J. A. M. A. **123**: 325, 1943.
7. Marshall, E. J., Jr., Litchfield, J. T., Jr, White, H. J., Bratton, A. C., and Shepherd, R. G.: J. Pharmacol. & Exper. Therap. **76**: 226, 1942.
8. Schmidt, L. H., Sesler, C. L., and Hughes, H. B.: J. Pharmacol. & Exper. Therap. **81**: 43, 1944.
9. Schmidt, L. H., Hughes, H. B., Badger, E. A., and Schmidt, I. G.: J. Pharmacol. & Exper. Therap. **81**: 17, 1944.
10. Bratton, A. C., and Marshall, E. K., Jr.: J. Biol. Chem. **128**: 537, 1939.
11. Goldring, D., Maxwell, R., and Hartmann, A. F.: J. PEDIAT. **26**: 1, 1945.
12. Gilligan, D. R.: J. Pharmacol. & Exper. Therap. **79**: 320, 1943.
13. Barnett, H. L., Perley, A. M., Forbes, G. B., and Goldring, D.: Am. J. M. Sc. **206**: 599, 1943.

THE PREVENTION OF EDEMA IN INFANTS UNDERGOING SULFONAMIDE TREATMENT

ROBERT KLEIN, M.D.
BOSTON, MASS.

IT HAD been noted for some time at the Children's Hospital that infants treated with sulfonamides and adjuvant alkalies became edematous more often than might be expected from the incidence of pulmonary infections. Upon closer examination it was noted that even in the absence of frank pitting edema, many other infants made precipitous and appreciable weight gains, which were as rapidly lost upon recovery and cessation of therapy. It has long been a well-recognized observation that patients with pneumonia very frequently became edematous and a diuresis was hailed as the first sign of recovery. However, with the advent of the sulfonamides this was noted more often in pulmonary infections and also, interestingly enough, was seen in other infections. The alkali in general use in the Children's Hospital, as elsewhere, was sodium bicarbonate.

Because of the well-known importance of the sodium ion in water balance, it was decided to see whether the edema could be prevented by using alkalies with cations other than the sodium ion. Potassium citrate was chosen because of its high solubility and availability at the time. Without selection, alternating admissions requiring sulfonamide therapy were given either sodium bicarbonate or potassium citrate.

The dosage of the sodium bicarbonate ranged from 0.28 to 0.42 Gm. per kilogram. The dose of potassium citrate ranged between 0.44 to 0.70 Gm. per kilogram. In the administration of the drugs the larger doses were given the smaller infants. After this series, a group of children were given a mixture of sodium bicarbonate and potassium citrate. This mixture contained .066 Gm. of potassium citrate and .033 Gm. of sodium bicarbonate in each cubic centimeter. The average dose was 0.42 Gm. of potassium citrate and 0.21 Gm. of sodium bicarbonate per kilogram of body weight. This mixture was used in an attempt to lessen the theoretical chances of toxicity due to the potassium ion and at the same time to obviate the production of edema due to excess sodium. A fourth group was given 10 per cent sodium lactate in dosage of 0.48 Gm. per kilogram of body weight as the alkalinizing agent. The apparent discrepancies in amount of alkali used do not really exist. This is made clear by stating the dosage in moles of cation used per kilogram of body weight. Examples of this are given in Table I. All the alkalies were given by mouth. Very few children were unable to take them in this manner. These infrequent patients are customarily given parenteral one-sixth molar sodium lactate. The pH of the urine was measured with nitrazine paper three times a day. All the alkalies tried, in the dosages given, satisfactorily kept the pH of the urine between 7 and 7.5 or better,

From the Department of Pediatrics, Harvard Medical School and the Department of Medicine of the Children's and Infants' Hospitals.

as measured by the nitrazine paper method of testing pH. The shortcomings of this method are well known but do not need to concern us here.

No evidence of potassium intoxication was noted on electrocardiograms of four of the patients given potassium citrate. None of the infants gave evidence of any sulfonamide damage to their kidneys.

Only those patients who had frank pitting edema as well as marked sudden weight gains were classified as edematous. The number of infants given each alkali and the number of each group that became edematous are given in Table I. Of those that became edematous three were diagnosed as having bronchopneumonia or interstitial pneumonia; two had bronchiolitis; one had influenza; two had meningitis; one had roseola infantum; and the other two had pyrexia of unknown origin as their initial diagnoses. The final diagnoses of the last two were neurological disorders.

TABLE I

DRUG	NO. PATIENTS	NO. PATIENTS WITH EDEMA	AVERAGE DOSE PER KILOGRAM OF BODY WEIGHT	MOLES OF CATION PER KILOGRAM WEIGHT
$NaHCO_3$	23	6	0.28-0.42 Gm.	.0033-.005
Na lactate	11	2	0.48 Gm.	.0043
TOTAL	34	8		
$NaHCO_3$ and K citrate	23	3	0.42 Gm. of K citrate and 0.21 Gm. of $NaHCO_3$	
K citrate	31	0	0.44-0.70 Gm.	.004-.006

In more than one-half of the patients who developed edema, the edema developed at a time when the pH of the urine was below 7.0. Generally, with the subsidence of edema the urine would become alkaline. The edema would reach its peak in from one to two days. The patient frequently gained as much as a pound in this period and then would gain little or no more. As a rule, there would be little fluctuation in weight after the initial precipitous rise till the subsidence of the edema. The loss in weight generally was rapid, requiring from three to five days. In one instance, the edema disappeared while the patient was still on the sodium-containing alkali; in the rest it did not disappear until the alkali was omitted with or without potassium citrate being substituted for it. It is not known what the diuretic effect of the potassium was, because urinary collections for volumetric determinations are so difficult in infants. No attempt was made to determine the effect of the potassium alkali on the level of sulfonamide in the blood since there are so many variables, such as speed of absorption and time of collecting blood sample in relation to time of administration, that govern the blood level of sulfonamide. However, Peterson, Goodwin, and Finland have shown that the pH of the urine is probably more important than the volume in determining the amount of excretion of sulfonamide.[1]

No advantage for potassium citrate was noted in older children as clinical edema has not been a problem here. Its use as adjuvant therapy with sulfonamide treatment of infections occurring in cases of the nephrotic syndrome is obvious. It should be stated, however, that its value seems to be entirely a negative one. That is, it does not add to the edema as does sodium bicarbonate.

On the other hand, it does not seem to have any diuretic action in nephrosis although it has been tried in large doses in the past. In fact, nephrotic children occasionally have had a diuresis after potassium citrate is stopped. This may well have been due to cessation of sulfonamide therapy and recovery from infection which were coincident to stopping potassium citrate administration. This last is further borne out by one nephrotic patient who was given potassium citrate alone and did not have the response that was seen when this drug was administered to similar patients with sulfonamides in the presence of infection.[2]

Potassium bicarbonate has also been used with sulfonamides in the treatment of infections in the presence of congestive failure by Ohnysty and Wolfson.[3]

Nephritis, nephrosis, and other kidney diseases per se are not contraindications to the use of potassium-containing alkalies, but it cannot be emphasized too strongly that anuria is a contraindication. Although the amounts of potassium ion administered in the two cases reported by Finch and Marchand[4] were far in excess of the ordinary dosage reported here, these two cases of potassium poisoning in anuria show the possible dangers in cases of anuria.

Thus, it would seem that the substitution of alkalies containing the potassium ion instead of sodium as the cation results in a significant lessening of the incidence of edema. It would seem reasonable to believe that the added burden of edema from sodium retention due to the use of sodium-containing alkalies might prove embarrassing to the patient.

REFERENCES

1. Peterson, O. L., Goodwin, R. A., Jr., and Finland, M.: J. Clin. Investigation 22: 659, 1943.
2. Janeway, C. A., and Hutchins, G.: Personal communication to author.
3. Ohnysty, J., and Wolfson, W. Q.: New England J. Med. 231: 381, 1944.
4. Finch, C. A., and Marchand, J. F.: Am. J. M. Sc. 206: 507, 1943.

INCIDENCE OF REACTIONS TO SULFONAMIDE DRUGS IN INFANTS AND CHILDREN

HERBERT WILLIAM FINK, M.D., AND CLEMENT A. SMITH, M.D.
DETROIT, MICH.

A REVIEW of the literature[1-18] on toxicity associated with sulfonamide administration reveals the average incidence to be about 5 per cent among patients of all age groups. Some reports[2] place the incidence of toxic reactions as high as 25 per cent; other reports[4] describe it in only 2 per cent of the cases studied. This paper deals with observations on the frequency and character of such reactions in more than 5,000 infants and children receiving sulfonamide drugs on the wards of the Children's Hospital of Michigan during a period of two and one-half years from 1942 to 1944. Chemotherapy was so extensively used at this time that the total number of 5,000 is based not on actual count but upon extension of statistics covering sample periods scattered throughout the whole two and one-half years. The figure is considered to be a conservative estimate. During this period of observation and in this number of administrations, sixty cases of drug fever (twenty-five with accompanying rashes), two cases of malignant neutropenia, two cases of hemolytic anemia, and four cases of anuria were encountered. Thus, the total incidence of important complications in this series was sixty-eight, or less than 1.4 per cent of the children treated. Statistical data on hematuria as a renal complication were also compiled for a survey period of one year, during which time over 1,500 patients received sulfonamide therapy. Significant renal disturbances occurred in ten instances, or less than 1 per cent of these cases.

Most of the patients studied received sulfadiazine. Early in the series some patients received sulfathiazole, and during one six-month period sulfamerazine was used extensively. The usual dosage of sulfadiazine and sulfathiazole employed was ½ grain (32 mg.) per pound (454 Gm.) as an initial dose, and a maintenance dosage of 1 grain (64 mg.) per pound per twenty-four hours, divided into four or six equal doses. The sodium salt was used for parenteral and occasional oral administration in slightly smaller dosage. The maintenance dosage of sulfamerazine was from ½ to ¾ grain (32 to 48 mg.) per pound per day.

TYPES OF UNTOWARD REACTIONS

The types of untoward reactions observed are grouped for convenience according to the effects produced by the drugs on the various body systems and the body in general (Table I).

1. *Gastrointestinal.*—As nausea and vomiting so frequently accompany acute illness in children it was not always possible to determine whether such manifestations resulted from the disease or the drug. However, it was the rule

From the Children's Hospital of Michigan and Department of Pediatrics, Wayne University College of Medicine.

Much of the sulfadiazine and sulfamerazine used in this study was generously provided by the Lederle Laboratories, Pearl River, N. Y.

TABLE I. UNTOWARD REACTIONS TO THE SULFONAMIDES

1. *Gastrointestinal.*—Nausea and vomiting (first to second day of administration)
2. *Renal.*—Hematuria, oliguria, anuria (first week)
   a. mechanical obstruction by crystals
   b. toxic
3. *Neurologic.*—Mental disturbances (first to second day)
4. *Blood and blood-forming organs.*—Leucopenia, anemia, hemolytic anemia, jaundice, purpura (first to second week)
5. *Systemic.*—Fever, with or without rash, occurring alone or in combination with any of the above reactions
   a. *Initial administration:* Fever with or without rash (fifth to ninth day)
   b. *Subsequent administration:* Fever usually with rash (first twenty-four hours)

to find that the gastrointestinal disturbances disappeared as the illness was brought under control, despite continuation of sulfonamide therapy. No vomiting occurred in any of the children receiving sulfonamides at a time when they were free from disease. Whenever vomiting from any cause interfered with oral administration, parenteral routes were found quite satisfactory and in many instances were the preferred methods of administration.

2. *Renal Complications.*—Renal reactions such as hematuria, oliguria, and anuria comprise over 50 per cent of the reported cases of drug reaction in the literature.[1-3, 19-33] Two main types of renal reactions have been described.[23, 24, 29, 30] In the one, the process is apparently mechanical; crystals, usually of the less soluble acetylated forms, cause bleeding by irritation of the renal endothelium, or plugs of crystals obstruct the kidney tubules or even the ureters. In the second type, the drug produces toxic effects on the kidney parenchyma; histologically areas of focal necrosis are seen along with degenerative changes in the tubules. These changes may be accompanied by similar necrotic changes in other organs and have been thought by some writers to be evidences of drug sensitivity.[21, 29, 34-36] Significant parenchymal damage to the kidney was not found in over 300 autopsies on children who received sulfonamides prior to death, and in only one case was there severe diffuse degenerative change in the tubules.*

In general, untoward effects of drug therapy upon the kidney have proved much less troublesome in children than in adults. As already stated, only for the last twelve-month period of this study are statistics available on the occurrence of gross hematuria. Over 1,500 children received sulfonamides during this time, and of this number ten showed gross hematuria (0.6 per cent). Microscopic hematuria was infrequently observed, and in only a few patients did it seem necessary to discontinue the drug because of this latter occurrence. The presence of sulfonamide crystals alone in the urine was not considered a reason to discontinue the drug.

Hematuria, when encountered, was seen most frequently during the first two or three days of therapy when larger than usual doses were given over a short period of time. Whenever microscopic hematuria was discovered, the drug was either temporarily discontinued for one or two doses, or the dosage reduced and fluid intake increased orally or parenterally. Drug treatment was then

*Dr. W. W. Zuelzer examined all pathologic material.

continued in the absence of further complications. In the presence of gross hematuria or the continuance of microscopic hematuria despite the measures stated, drug administration was always stopped. If resumption of the drug was considered necessary, smaller dosage was employed and large amounts of fluids were given usually with success. The occurrence of hematuria alone does not preclude re-employment of the drug in subsequent infections.

The development of oliguria and anuria, either preceded or accompanied by hematuria, was considered a danger signal calling for immediate cessation of drug therapy. During the entire period of observation, four cases of actual anuria were encountered. Two of these responded to therapy and recovered without any apparent permanent kidney damage; both of the remaining cases were fatal. In both of the latter instances sulfathiazole had been employed. One child, 5 years old, died in uremia after nine days of treatment with the usual 1 grain per pound per day dosage. The autopsy disclosed many congenital urinary anomalies with secondary obstruction and hydronephrosis. Accumulations of sulfonamide crystals were found blocking the calices and ureters. The second child, 11 months old, also showed at autopsy ureters completely blocked by plugs of crystals. He had received 1 grain per pound per day dosage for seven days. In both of the anuric cases with recovery (patients aged 1½ and 10 years), ureteral catheterizations were performed. In neither case was any obstruction encountered, but in each a small amount of syrup-like, bloody urine was obtained from the kidney pelvis. No crystals were found on microscopic examination of the urine. Despite the absence of obstruction, the catheters were left in place and shortly afterward urine flow began, so that the procedure may have been beneficial. Thus, it is of interest that the two fatalities seemed to be traceable to mechanical blockage, while the two cases with recovery were not proved to be obstructive. No child died as a result of renal damage from sulfadiazine or sulfamerazine.

Therapy in renal complications has thus been directed toward reducing the concentration of the drug in the urine and insuring an adequate urinary flow. In infants, a fluid intake of 2½ to 3 ounces (75 to 90 c.c.) of fluid per lb. per day was considered necessary. Older children received 40 to 80 ounces (1,200 to 2,400 c.c.) of fluid daily. Because of the marked infrequency of kidney complications in this series, it has not been thought necessary to supplement therapy by the routine administration of alkali.[15] The use of alkali in pediatric patients introduces difficulties in forcing children to take the relatively large amounts of soda (10 to 20 Gm. daily) needed to render the urine effectively alkaline.[20, 37] In addition, the tendency of alkali medication to produce refusal of oral fluids argues against the routine use of alkaline drugs.

3. *Neurologic.*—What part the sulfonamide drugs play in the production of mental disturbances is difficult to assess, since in the early stages of acute illness children often display drowsiness, increased irritability, confusion, and even delirium. These evidences of central nervous system disturbance tend to clear up with improvement in the child's condition, even though drug administration is continued. In only two instances was it necessary to discontinue the drug because of delirium. Severe neurologic disturbances such as polyneuritis and optic atrophy were not encountered.

4. *Blood and Blood-Forming Organs.*—The incidence of leucopenia (white blood cell count below 5,000 per cubic millimeter) is variously reported as between 2 per cent and 3 per cent.[1, 4, 19, 22, 24, 48] Whenever marked leucopenia (3,500 or less) was observed in this study, drug fever and rash were usually present also, indicating a sensitivity reaction. Leucopenia of this degree was rarely seen, and in eight cases in which serial counts were made, discontinuance of drug therapy resulted in a rapid rise of white cells. Two cases of malignant neutropenia were observed; in both, cells of the granulocytic series almost entirely disappeared from the blood. The subjects were infants who had been receiving sulfonamides for several weeks. With cessation of drug therapy and the employment of blood transfusions, neutrophilic cells reappeared and the white blood cell count was gradually restored to normal. Counts of 4,000 to 5,000 white blood cells per cubic millimeter were not considered an indication for stopping the sulfonamides, since most such counts returned to normal even though drug therapy was continued. In these instances, daily counts were recommended, and if the leucopenia progressed under such observation the drug was then discontinued.

Relatively few cases of hemolytic anemia due to sulfadiazine have been reported by others.[29] Two cases occurred in this series (both accompanied by fever). In these children symptoms began on the second and third days of drug administration, respectively. Drug therapy was discontinued and blood transfusions were given, with prompt recovery. Jaundice was present in these two patients but was encountered in no others. In no other patient were signs of hepatic insufficiency demonstrated. Purpura developed in one patient, but whether or not it was due to drug therapy could not be definitely ascertained. It can, therefore, be concluded that serious hematologic complications of sulfonamide therapy are infrequent in infants or children. When they do occur, other evidences of toxicity, such as fever and rash, are usually present as well.

5. *Systemic Effects.*—

A. *Initial Administration:* The occurrence of fever, with or without rash, generally indicates the development of what may be termed a toxic reaction. However, this does not necessarily mean that the patient has acquired permanent sensitivity to the drug, as will be shown. The reports of other authors indicate the incidence of any fever to be from about 2 to 10 per cent.[1-18] In this study sixty febrile reactions were encountered, an incidence of 1.2 per cent. Twenty-five of these patients had accompanying rashes.

The term "febrile reaction" indicates the development during drug administration of a temperature elevation which cannot be satisfactorily explained

TABLE II. TOXIC FEBRILE REACTIONS TO SULFONAMIDES

TOXIC FEBRILE REACTIONS	SULFADIAZINE	SULFATHIAZOLE	SULFAMERAZINE
No. cases fever alone	27	7	1
No. cases fever with rash	19	6	0
Total no. febrile reactions	46	13	1

(These figures do not represent a comparison of the toxic effects of the various drugs. Since most of the patients were given sulfadiazine, the larger number of reactions occurred in this group.)

on the basis of the disease and which subsides after the drug is discontinued. It is obvious that not all such fevers are due to drug reactions, and that therefore the figure given may be in excess of the actual frequency.

Fever ascribed to the sulfonamide drugs generally began toward the end of the first week of therapy or during the second week, and persisted until the drug was stopped. The elevated temperature then usually fell abruptly or came down slowly over a period of forty-eight hours, and in all cases complete recovery followed. In a few cases, fever which did not develop until shortly after cessation of drug therapy was suspected of being of drug origin, but readministration of the drug never produced a second febrile reaction.

The rash, which was observed in almost one-half of these febrile reactions, usually appeared while the temperature was rising or shortly afterward. Skin eruptions occurring in the absence of fever were never proved to be of drug origin. Scarlatiniform or measleslike eruptions were most often seen. Diffuse redness of the pharynx often accompanied the rash and caused complaints of sore throat or difficulty in swallowing. The absence of exudate over the tonsils and the diffuseness of the enanthem helped to distinguish the reaction from scarlet fever, but in some instances the differentiation at first was quite difficult. Leucocytosis, with counts as high as 70,000, and with the percentage of polymorphonuclear cells over 90 per cent, was not unusual during the febrile episodes. Some cases showed moderate leucopenia. In all instances, the counts rapidly returned to normal after the drug was stopped. Only one case of a toxic reaction resulting from local drug application was met with in this series, despite frequent use of the drug for many types of skin infection. Exfoliative dermatitis and other severe dermatological conditions were not encountered.

B. *Repeated Administration:* In a previous paper Fink and Wilson[13] showed that there is little evidence of increased incidence of reactions in children during a second or subsequent course of the drug. Although several other authors have not confirmed this,[12, 39, 40] the majority of the reports[1, 3, 4, 6, 13, 17, 18] agree that a second course is not more toxic than the first. The material of the present study has not indicated a significant effect of one course of uncomplicated sulfonamide administration in sensitizing the patient against later administration of the same drug. However, patients who have shown a febrile reaction to a drug administered once are likely to have developed sensitivity to that drug and may react with fever and rash to its readministration.[11, 13, 38] This type of reaction develops almost always within forty-eight hours after a repeat dose and has been termed an "immediate" or hypersensitivity reaction. During the period of two and one-half years of this study, every patient who developed this "immediate" type of reaction had also shown a febrile reaction to a previous course of the drug. Apparently, then, the original temperature elevation may indicate the development of sensitivity. Consequently, if a complete history fails to disclose an earlier febrile reaction, a child cannot be considered sensitized, and second and subsequent courses then can be given without fear of an immediate reaction.

In an attempt to determine whether or not febrile reactions always mean the establishment of sensitivity, thirty-four children who showed otherwise

TABLE III. REACTIONS TO REPEAT DOSES OF SULFONAMIDES

	INITIAL REACTION—FEVER ONLY				INITIAL REACTION—FEVER AND RASH				GRAND TOTAL
	SULFADIAZINE	SULFATHIAZOLE	SULFAMERAZINE	TOTAL	SULFADIAZINE	SULFATHIAZOLE	SULFAMERAZINE	TOTAL	
Total number cases retested with drug producing fever	9	3	1	13	18	2	1	21	34
No reaction to test dose	5	2	1	8	5	2	1	7	15
Immediate reaction fever only	3	0	0	3	0	0	0	0	3
Immediate reaction fever and rash	1	1	0	2	13	1	0	14	16
Total immediate (hypersensitivity) reactions	4	1	0	5	13	1	0	14	19

unexplained temperature elevation during initial courses of one of the sulfonamides were deliberately given repeat courses. The usual test dose was 0.25 Gm. (grains 3.8) given orally. If no reaction occurred to the first repeat dose, the drug was in most instances administered for forty-eight to seventy-two hours, if necessary. Most of the tests were performed within two weeks of the original reaction.

In thirteen of the thirty-four children thus tested a rash had not been observed during the original febrile reaction. Of these thirteen children, eight showed no untoward response to the test exhibition of the same drug, and these children were therefore not considered to have become sensitized to the drug. Only two reacted with fever and rash, while three showed fever only.

Of the twenty-one children who had shown fever and rash at the original reaction, only seven showed no response to the test doses. All of the remaining fourteen quickly developed both fever and rash. All the children responding with fever and rash did so within eight hours after the test was given. Those responding with fever alone did so in from twenty-four to forty-eight hours.

It would therefore appear that slightly over one-half of the children showing febrile reactions to sulfonamide drugs may coincidentally be sensitized to the drug, as manifested by the production of an "immediate" type of response on readministration. If the initial fever is accompanied by rash, the chances of sensitization are even greater.

Test doses of a different sulfonamide were given in nine instances to seven children. Five of the children reacting to test doses of sulfadiazine were tested with sulfathiazole. Two developed reactions. One of these was given sulfamerazine without eliciting any response, and the other received sulfapyridine without reaction. Two children reacting to sulfathiazole did not show any untoward effect from sulfadiazine administration. Further work is necessary to determine how much cross-sensitization can occur, but apparently a different sulfonamide is less likely to produce a reaction than the original one in sensitized children.

From these observations, it is concluded that sulfonamides can be safely readministered to children who have shown no previous reactions; whereas if a

child has once shown a toxic reaction, the probability is that subsequent administration will produce further and more immediate difficulty. Under such circumstances a different sulfonamide may be tried if readministration of a sulfonamide is considered therapeutically essential, as there is some evidence that it may be better tolerated. A test dose of 0.25 Gm. (grains 3.8) will usually reveal the presence of sensitivity. In the event of cross-sensitization, the use of sulfonamides must be abandoned, and other therapeutic agents such as penicillin should be used where effective.

OBSERVATIONS ON SULFONAMIDE SENSITIVITY

Merkel and Crawford,[23] Lederer and Rosenblatt,[24] Geever,[21] and others have all reported findings on patients dying as the result of sulfonamide administration. Most of the deaths were of renal origin, but a majority also showed toxic febrile reactions, along with the renal reactions. The outstanding finding in all cases was the presence of areas of focal necrosis in the kidney, as well as in the liver, spleen, lungs, brain, and heart, indicating widespread damage. Rich[34-38] has found similar areas of necrosis in his study of autopsy material. However, his findings were made not only on patients receiving sulfonamides without reaction, but also on patients who had received horse serum but whose deaths were not due to any serum reaction. Rich has demonstrated that the areas of necrosis are the result of periarteritis nodosa-like lesions which he believes may be manifestations of sensitivity, not only to sulfonamides but also to serum, bacterial protein, and the like. The lesions are analogous to those in the commonly observed Arthus phenomenon.

French and Weller,[41] in a review of 283 autopsies on patients who had received sulfonamide drugs but in whom death had not been due to drug toxicity, found interstitial myocarditis in 126 cases. Rich has postulated that such changes are similar to those of periarteritis nodosa. The significance of these observations is not quite clear, and further reports will be awaited with much interest. In autopsy findings in more than 300 patients who had received sulfonamides at the Children's Hospital of Michigan, no instance of significant interstitial myocarditis has been found, and in no case has the presence of areas of focal necrosis been demonstrable.

Several investigators[42-46] have reported the results of experiments attempting to explain the mechanism of sensitization. Wedum,[42, 43] and Gerber and Gross[45] have demonstrated that experimental animals can be sensitized to protein conjugated with sulfonamide. By using the conjugated protein as the antigen, they have elicited positive skin reactions in experimentally sensitized animals and have produced anaphylactic shock by its intravenous injection. Use of the unconjugated sulfonamide failed to produce a reaction in animals, and attempts to produce skin reactions in sensitized human beings were unsuccessful. However, Leftwich[47] reported that by using blood serum from patients receiving sulfonamide drugs, and therefore containing protein-bound sulfonamide, he could produce positive skin tests in sensitized patients. Burton, Wheeler, and one of us[49] have been unable to elicit positive skin tests in children by this method. At present, we believe that the only certain way to demonstrate sensi-

tivity among pediatric patients is by observing the effects of oral readministration of the drug. A test dose of 0.25 Gm. (grains 3.8) is generally sufficient to produce a reaction in a truly sensitized child.

SUMMARY

In a study of more than 5,000 infants and children receiving sulfonamide drugs on the wards of the Children's Hospital of Michigan during a period of two and one-half years from 1942 to 1944, the following observations were made:

1. Sulfonamides may produce or aggravate gastrointestinal and neurologic disturbances in acutely ill children. Such reactions were rarely noted in children receiving chemotherapy during convalescence or at a time when they were well.

2. Renal complications were rare and apparently less frequently encountered than in adults. Two deaths from anuria not associated with crystalluria occurred in this series.

3. Untoward effects on the blood and blood-forming organs were also uncommon in children and when present were usually associated with evidences of a general reaction such as fever and rash. Two cases of malignant neutropenia and two cases of hemolytic anemia were encountered; all patients recovered.

4. Sixty patients (1.4 per cent) developed febrile reactions, twenty-five with accompanying rashes. Leucocytosis with white blood cell count as high as 70,000 often occurred during the reaction, although leucopenia was occasionally seen. All patients completely recovered following cessation of drug therapy.

5. Over one-half (59 per cent) of the patients reacting to one course of sulfonamide developed "immediate" reactions to tests with repeat doses. Test doses of 0.25 Gm. (grains 3.8) were usually sufficient to produce a reaction.

6. "Immediate" reactions were observed only in those patients who had shown previous drug reactions.

7. Seven children were given test doses of a sulfonamide different from that to which they were proved sensitive. Only two developed reactions, and both of these received a third sulfonamide without reaction.

8. Observation of the patient after oral administration of a test dose of 0.25 Gm. (3.8 grains) of sulfonamide is recommended as a test for suspected drug sensitivity.

9. Skin testing of suspected sulfonamide sensitive patients with human sulfonamide-containing serum after the manner of Leftwich has not proved useful in children.

CONCLUSIONS

Untoward reactions to sulfonamides are infrequent in infants and children and rarely cause serious effects. Such patients are apparently not easily sensitized. Since danger of severe reaction to subsequent sulfonamide administration exists only when a febrile reaction has occurred previously, there is apparently no greater reason to fear harmful effects from multiple courses of drug therapy

than from the first course. Because of the low incidence of toxic reactions, sulfonamides should not be withheld from infants or children because of fear of producing an untoward response.

REFERENCES

1. Wheeler, C., and Plummer, N.: Ann. Int. Med. **16**: 269, 1942.
2. Applebaum, E., and Nelson, J.: Am. J. M. Sc. **207**: 492, 1944.
3. Clark, J. K., Flippin, H. F., and Murphy, F. D.: Am. J. M. Sc. **205**: 846, 1943.
4. Plummer, N., and Wheeler, C.: Am. J. M. Sc. **207**: 175, 1944.
5. Frist, T. F.: War Med. **5**: 150, 1944.
6. Siegel, M.: Am. J. Dis. Child. **68**: 23, 1944.
7. Drake, M. A.: J. A. M. A. **124**: 1020, 1944.
8. Fox, F. E., and Chiller, A. A.: U. S. Nav. M. Bull. **42**: 923, 1944.
9. Johnson, R. D.: J. A. M. A. **124**: 979, 1944.
10. Murphy, F. D., Kuzma, J. F., Polley, T. Z., and Grill, J.: J. A. M. A. **124**: 799, 1944.
11. Long, P. H.: J. A. M. A. **121**: 303, 1943.
12. Lyons, R. H., and Balberor, H.: J. A. M. A. **118**: 955, 1942.
13. Fink, H. W., and Wilson, J. L.: J. PEDIAT. **22**: 513, 1943.
14. Keefer, C. S.: New England J. Med. **226**: 266, 1942.
15. Vilter, C. F., and Blankenhorn, M. A.: J. A. M. A. **126**: 691, 1944.
16. Schlesinger, E. R., and Mitchell, U. L., Jr.: Am. J. Dis. Child. **56**: 1256, 1938.
17. Talbot, R. R., Jr., and Adcock, J. D.: Am. J. M. Sc. **205**: 841, 1943.
18. Green, R. C., Steckel, M. L., and Michener, J. M.: Mil. Surgeon **93**: 399, 1943.
19. Finland, M., Peterson, O. L., and Goodwin, R. A.: Ann. Int. Med. **17**: 920, 1942.
20. Fox, C. L., Jr., Jensen, O. J., Jr., and Mudge, G. H.: J. A. M. A. **121**: 1147, 1943.
21. Geever, E. F.: Am. J. M. Sc. **207**: 331, 1944.
22. Dowrie, J. O., and Abramson, M. H.: J. PEDIAT. **24**: 176, 1944.
23. Merkel, W. C., and Crawford, R. C.: J. A. M. A. **119**: 770, 1942.
24. Lederer, M., and Rosenblatt, P.: J. A. M. A. **119**: 8, 1942.
25. Rake, G., Van Dyke, H. B., and Corwin, W. C.: Am. J. M. Sc. **200**: 353, 1940.
26. Antopol, W., Lehr, D., Churg, J., and Sprinz, H.: Arch. Path. **31**: 592, 1941.
27. Bradford, H. A., and Shaffer, J. H.: J. A. M. A. **119**: 316, 1942.
28. Wright, D. O., and Kinsey, R. E.: J. A. M. A. **120**: 1351, 1942.
29. Duff, G. L., Murray, E. G. D.: Am. J. M. Sc. **205**: 439, 1943.
30. Ormond, J. K., and Roth, R. B.: J. Urol. **51**: 92, 1944.
31. Winters, K. J., and Janney, F. R.: Am. J. Dis. Child. **65**: 702, 1943.
32. Murphy, F. D., and Wood, W. D.: Ann. Int. Med. **18**: 999, 1943.
33. Murphy, F. D., Kuzma, J. F., Polley, T. Z., and Grill, J.: Arch. Int. Med. **73**: 433, 1944.
34. Rich, A. R., and Gregory, J. E.: Bull. Johns Hopkins Hosp. **72**: 65, 1943.
35. Rich, A. R.: Bull. Johns Hopkins Hosp. **71**: 123, 1942.
36. Rich, A. R.: Bull. Johns Hopkins Hosp. **71**: 375, 1942.
37. Rohr, J. H., and Christopher, F.: Surg., Gynec. & Obst. **78**: 515, 1944.
38. Garvin, C. F.: J. A. M. A. **113**: 288, 1939.
39. Dowling, H. F., Dumoff, S. E., Lepper, M. H., and Sweet, L. K.: J. A. M. A. **125**: 103, 1944.
40. Dowling, H. F., and Lepper, M. H.: Am. J. M. Sc. **207**: 349, 1944.
41. French, A. J., and Weller, C. V.: Am. J. Path. **18**: 109, 1942.
42. Wedum, A. G.: J. Infec. Dis. **70**: 173, 1942.
43. Wedum, A. G.: J. Bact. **41**: 64, 1941.
44. Abernethy, T. J., and Bukantz, S. C.: J. Clin. Investigation **20**: 433, 1941.
45. Gerber, I. E., and Gross, M.: J. Immunol. **48**: 103, 1944.
46. Davis, B. D.: J. Clin. Investigation **22**: 753, 1943.
47. Leftwich, W. B.: Bull. Johns Hopkins Hosp. **74**: 26, 1944.
48. Flippin, H. F., Rose, S. B., Schwartz, L., and Domm, A. H.: Am. J. M. Sc. **201**: 585, 1941.
49. Wheeler, W. E., Burton, I., and Fink, H. W.: Observations on Skin Testing for Sensitivity to Sulfa Drugs in Children. Unpublished data.

TABLES FOR PREDICTING ADULT HEIGHT FROM SKELETAL AGE AND PRESENT HEIGHT

NANCY BAYLEY, PH.D.
BERKELEY, CALIF.

BEING exceptionally tall or short, in comparison with other children the same age, is often a matter of concern for children or their parents. For this reason the extent of epiphyseal closure is often investigated roentgenographically in order to determine likelihood of future growth and to estimate the extent to which further growth may occur. In a more limited field, surgeons have been interested in such estimates, in predicting the effect of growth in certain forms of osteotomy. Recent studies carried out at the University of California on the relation of growth to skeletal age indicate that it is possible to estimate, within certain limits of error, the probable adult height of children whose growth is still incomplete.[1]

Individual differences in velocities of maturing result in widely varying degrees of maturity among any random sample of children the same age, especially during adolescence. But velocities of maturing are not simply related to growth in size.[2] Children who mature early follow a different course of growth than children who mature late. Furthermore there are sex differences in the patterns of growth of early and late maturers. In general, for both sexes, there are two factors which influence growth. (1) During childhood, the mere differences in velocity of maturation make the rapid maturers large for their age and the slow maturers small. But (2) the longer the period of time a person is in the process of growing (that is, epiphyses open and healthy growth factors operating), the more opportunity he has for growth. Therefore, though slow maturers are small for their age, they tend, actually, to be large for their skeletal age, while the rapid maturers, though large for their chronological age, tend to be small for their skeletal age.

In girls some factor, probably related to the female sex hormones, stops growth rather abruptly after menarche. As a result we find that early maturing girls are usually large when young, slowing down to about average in height at 13 years, and completing their growth rapidly, to become small adults. Late maturing girls, conversely, are more often small when young, catch up to the average at about 13 and become tall adults.

Early maturing boys do not exhibit this abrupt curtailment of growth but slow down more gradually, and they seem to have a normal likelihood of becoming tall, or average, or short adults. Late maturing boys continue to grow, some even into their early twenties, and more often than not they become tall adults. Because of further differences in body build of early and late maturing boys, the late maturers, while young, are at a considerable disadvantage, physically: the early maturers tend to be large and broad-built or heavy-set at all ages, while the late maturers are usually slender and long-legged, their greater adult height being due primarily to continued growth of the legs.

From the Institute of Child Welfare, University of California.

Because of these characteristic differences between children growing at different velocities, predictions of their adult height will be more nearly accurate if determined for each group separately.

Tables designed to facilitate estimates of adult height are presented here, for boys and girls, between the ages of 7 years and maturity. These tables are constructed from data from two sources, Massachusetts children observed in the Harvard Growth Study* and the California children studied at the Institute of Child Welfare of the University of California.

To secure a measure of relative growth each child's height at any given time was expressed as a percentage of his own adult stature as measured after closure of the epiphyses of the bones in his hand, wrist, and knee.† When this was done, the per cent of mature height attained was found to be very closely related to skeletal age as determined by the Todd standards.[3] This relationship to skeletal age was found to be much closer than to chronological age. It is reasoned, therefore, that if we wish to predict adult height, the prediction will be much more accurate if a child's skeletal age is taken into account in making the estimate. This is especially true during the early teens when differences in physical maturity contribute so largely to differences in children's heights. In using these tables, it must be remembered that this system of predictions is based on measurements of normal children. We cannot expect it to be applicable to cases of extreme deviation in which the regulators of growth are not functioning normally.

The tables have been constructed to facilitate the process of computing predicted height. In order to predict a child's mature height it is necessary to have an assessment of his skeletal age (based on x-rays which have been compared with standards such as those of Todd[3] or Flory[4]), and his height, measured at the time the x-rays were taken. For the younger ages it is necessary, in addition, to have the child's chronological age, because age must be taken into account when a child is retarded or accelerated in a marked degree. Therefore, separate tables have been constructed for children under twelve years who deviate widely from their age norms.

DIRECTIONS FOR USING THE PREDICTION TABLES

First, select the correct table for the child's sex, skeletal age, and degree of acceleration or retardation. (Because girls mature more rapidly than boys, the difference during adolescence amounting, on the average, to two years, it is

*Shuttleworth, F. K.: Data on the Growth of Public School Children (From the Materials of the Harvard Growth Study). *Monographs of the Society for Research in Child Development*, 14: 136, 1938. From these published records we selected approximately 100 boys and 100 girls of North European stock, for whom there were records (of chronological age skeletal age, and height) extending from 6 or 7 years to maturity. It was necessary to include some boys whose epiphyseal closure was not quite complete, extrapolating for probable final stature. Todd Skeletal Ages recorded were evidently two months older than those finally published in Todd's Atlas, and therefore two months were subtracted from each skeletal age, in order to make these records directly comparable to the California material and to the Todd published standards.

†The method and results are described in detail in Bayley, N.: Skeletal Maturing in Adolescence as a Basis for Determining Percentage of Completed Growth, Child Development, 14: 1, 1943. The Harvard Growth Study data are based on hand x-rays only. Some ephiphyses close later than those in either hand or knee, and for this reason there may often be slight growth, usually of the trunk, after these areas are mature. Such growth, however, when it does occur is rarely more than one-fourth inch, which is within the error of measurement.

important that a child be assessed on standards and tables for his or her own sex.) The boys' tables, numbered I, are divided for convenience of handling into two age groups, Table IA for skeletal ages (Sk.A.) below 13 years, and Table IB for those 13 years and above. Two additional tables take care of the younger boys whose skeletal ages deviate widely from their chronological ages. Table IC is for boys accelerated more than one year, if their skeletal ages are 12½ years or less. Table ID is for boys retarded more than one year, if their skeletal ages are 11¾ years or less. The girls' tables numbered II are similarly divided: Table IIA for girls with skeletal ages of 11 years or less, and Table IIB for those above 11 years. The supplementary tables for the younger, more deviate girls are: Table IIC for girls who are accelerated more than one year and with skeletal ages of 14 years or less; and Table IID for girls who are retarded more than one year and whose skeletal ages are under 12 years.

Once the correct table is selected the predictions may be read directly from the table. Find the column which represents the child's skeletal age and the line which represents his height. The figure in the square where the two intersect is his predicted mature height. For example, a 10½-year-old boy who is 57 inches tall and has a bone age of 11 years should be expected, from Table IA, to have a mature height of 70.4 inches. If, however, this boy's chronological age is 8 years, 9 months, he is accelerated more than one year and, according to Table IC, his expected adult height will be 72.0 inches. On the other hand, if he is 13 years, 3 months old, with this same height and skeletal age, we might (if we did not know his skeletal age) expect him to be a very short adult (64.6 inches, Table IB), instead of the more likely 69.3 inches predicted from Table ID.

ILLUSTRATIVE CASES

The close relationship of skeletal maturing to growth in height is illustrated in Tables III and IV and Figs. 1 and 2 for two girls whose skeletal ages are very deviate from their chronological ages. One patient (Case 6F) (Berkeley Growth Study[5]) is very mature for her age, and another (Case 1970) (Harvard Growth Study) is retarded in skeletal maturity. Tables III and IV give, for each of these cases, the age at every measurement with the corresponding skeletal age and height. From these measures we have computed the per cent of her mature height attained at each earlier age: these percentages are used in plotting the individual curves shown in Figs. 1 and 2 in relation to the group norms. The individual curves are presented together with the smoothed curve of the means for the groups from which the tables were constructed. The shaded area represents the percentages included within one standard deviation from the mean, or the middle 67 per cent of the cases.

The per cent of her own mature height achieved by Case 6F is (at most ages) far above the average for children her age (Fig. 1). Predicted height based on chronological age would be greatly overestimated. But when she is compared with children of the same skeletal age (Fig. 2) her curve is much closer to the group average. Case 1970 shows just the opposite trend, being retarded for her chronological age (Fig. 1) but not for her skeletal age (Fig. 2).

TABLE IA. FOR ESTIMATING MATURE HEIGHT OF BOYS, WITH SKELETAL AGES WITHIN ONE YEAR OF THEIR CHRONOLOGICAL AGES: SKELETAL AGES, 7 TO 13 YEARS

Skeletal Age	7-0	7-3	7-6	7-9	8-0	8-3	8-6	8-9	9-0	9-3	9-6	9-9	10-0	10-3	10-6	10-9	11-0	11-3	11-6	11-9	12-0	12-3	12-6	12-9
% of Mature Height	69.3	70.1	70.6	71.3	71.8	72.5	73.4	74.3	75.0	75.8	76.5	77.4	78.1	78.9	79.7	80.3	81.0	81.4	82.7	83.0	83.8	84.4	85.5	86.4
Ht. (inches)																								
42																								
43	62.0	61.3																						
44	63.5	62.8	62.3	61.7	61.3																			
45	64.9	64.2	63.7	63.1	62.7																			
46	66.4	65.6	65.2	64.5	64.1	63.4	62.7	61.9	61.3															
47	67.8	67.0	66.6	65.9	65.4	64.8	64.0	63.3	62.7	62.0	61.4	60.7												
48	69.3	68.5	68.0	67.3	66.9	66.2	65.4	64.6	64.0	63.3	62.7	62.0												
49	70.7	69.9	69.4	68.7	68.2	67.6	66.8	65.9	65.3	64.6	64.0	63.3	62.7	62.1	61.5	61.0	60.5							
50	72.2	71.3	70.8	70.1	69.6	69.0	68.1	67.3	66.7	66.0	65.4	64.6	64.1	63.4	62.7	62.3	61.7							
51	73.6	72.8	72.2	71.5	71.0	70.3	69.5	68.6	68.0	67.3	66.7	65.9	65.4	64.6	64.0	63.5	63.0	62.7	61.7	61.4	60.9			
52	75.0	74.2	73.7	72.9	72.4	71.7	70.8	70.0	69.3	68.6	68.0	67.2	66.7	65.9	65.2	64.8	64.2	63.9	62.9	62.6	62.1	61.6		
53	76.5	75.6	75.1	74.3	73.8	73.1	72.2	71.3	70.7	69.9	69.3	68.5	67.9	67.2	66.5	66.0	65.4	65.1	64.1	63.9	63.2	62.8		
54				75.7	75.2	74.5	73.6	72.7	72.0	71.2	70.6	69.8	69.2	68.4	67.8	67.2	66.7	66.3	65.3	65.1	64.4	64.0	63.2	62.5
55				77.1	76.6	75.9	74.9	74.0	73.3	72.6	71.9	71.1	70.5	69.7	69.0	68.5	67.9	67.6	66.5	66.3	65.6	65.2	64.3	63.7
56				78.5	78.0	77.2	76.3	75.4	74.7	73.9	73.2	72.4	71.8	71.0	70.3	69.7	69.1	68.8	67.7	67.5	66.8	66.4	65.5	64.8
57								76.7	76.0	75.2	74.5	73.6	73.1	72.2	71.5	71.0	70.4	70.0	68.9	68.7	68.0	67.5	66.7	66.0
58								78.1	77.3	76.5	75.8	74.9	74.4	73.5	72.7	72.2	71.6	71.3	70.1	69.9	69.2	68.7	67.8	67.1
59												76.2	75.6	74.8	74.0	73.5	72.8	72.5	71.3	71.1	70.4	69.9	69.0	68.3
60												77.5	76.8	76.1	75.3	74.7	74.1	73.7	72.6	72.3	71.6	71.1	70.2	69.4
61															76.5	76.0	75.3	74.9	73.8	73.5	72.8	72.3	71.3	70.6
62																	76.5	76.2	75.0	74.7	74.0	73.5	72.5	71.8
63																			76.2	75.9	75.2	74.6	73.7	72.9
64																				77.1	76.4	75.8	74.9	74.1
65																				78.3	77.6	77.0	76.0	75.2
66																				79.5	78.8	78.2	77.2	76.4

TABLE IB. FOR ESTIMATING MATURE HEIGHT OF BOYS, WITH SKELETAL AGES, 13 YEARS TO MATURITY

Skeletal Age	13-0	13-3	13-6	13-9	14-0	14-3	14-6	14-9	15-0	15-3	15-6	15-9	16-0	16-3	16-6	16-9	17-0	17-3	17-6	17-9	18-0	18-3	18-6	18-9
% of Mature Height	87.3	88.3	89.3	90.4	91.5	92.7	93.7	94.5	95.5	96.3	96.9	97.3	97.7	98.2	98.3	98.5	98.8	99.0	99.2	99.4	99.6	99.8	99.9	100
Ht. (inches)																								
54	61.9																							
55	63.0	62.3	61.6																					
56	64.1	63.4	62.7	61.9																				
57	65.3	64.6	63.8	63.0	62.3	61.5	60.8	60.3																
58	66.4	65.7	64.9	64.2	63.4	62.6	61.9	61.4																
59	67.6	66.8	66.1	65.3	64.5	63.6	63.0	62.4																
60	68.7	68.0	67.2	66.4	65.6	64.7	64.0	63.5	62.8	62.3	61.9	61.7	61.4											
61	69.9	69.1	68.3	67.5	66.7	65.8	65.1	64.6	63.9	63.3	63.0	62.7	62.4											
62	71.0	70.2	69.4	68.6	67.8	66.9	66.2	65.6	64.9	64.4	64.0	63.7	63.4											
63	72.2	71.3	70.5	69.7	68.9	68.0	67.2	66.7	66.0	65.4	65.0	64.7	64.5											
64	73.3	72.5	71.7	70.8	69.9	69.0	68.3	67.7	67.0	66.5	66.0	65.8	65.5	65.2	65.1	65.0	64.8	64.6	64.5	64.4	64.3	64.1	64.1	64.0
65	74.5	73.6	72.8	71.9	71.0	70.1	69.4	68.8	68.1	67.5	67.1	66.8	66.5	66.2	66.1	66.0	65.8	65.7	65.5	65.4	65.3	65.1	65.1	65.0
66	75.6	74.7	73.9	73.0	72.1	71.2	70.4	69.8	69.1	68.5	68.1	67.8	67.6	67.2	67.1	67.0	66.8	66.7	66.5	66.4	66.3	66.1	66.1	66.0
67	76.7	75.9	75.0	74.1	73.2	72.3	71.5	70.9	70.2	69.6	69.1	68.9	68.6	68.2	68.2	68.0	67.8	67.7	67.5	67.4	67.3	67.1	67.1	67.0
68	77.9	77.0	76.1	75.2	74.3	73.4	72.6	72.0	71.2	70.6	70.2	69.9	69.6	69.2	69.2	69.0	68.8	68.7	68.5	68.4	68.3	68.1	68.1	68.0
69	79.0	78.1	77.3	76.3	75.4	74.4	73.6	73.0	72.3	71.7	71.2	70.9	70.6	70.3	70.2	70.0	69.8	69.7	69.6	69.4	69.3	69.1	69.1	69.0
70	80.2	79.3	78.4	77.4	76.5	75.5	74.7	74.1	73.3	72.7	72.2	71.9	71.6	71.3	71.2	71.1	70.8	70.7	70.6	70.4	70.3	70.1	70.1	70.0
71					77.6	76.6	75.8	75.1	74.3	73.7	73.3	73.0	72.7	72.3	72.2	72.1	71.9	71.7	71.6	71.4	71.3	71.1	71.1	71.0
72						77.7	76.8	76.2	75.4	74.8	74.3	74.0	73.7	73.3	73.3	73.1	72.9	72.7	72.6	72.4	72.3	72.1	72.1	72.0
73						78.7	77.9	77.2	76.4	75.8	75.3	75.0	74.7	74.3	74.3	74.1	73.9	73.7	73.6	73.4	73.3	73.1	73.1	73.0
74							79.0	78.3	77.5	76.8	76.4	76.0	75.7	75.4	75.3	75.1	74.9	74.7	74.6	74.4	74.3	74.1	74.1	74.0
75															76.3	76.1	75.9	75.7	75.6	75.4	75.3	75.2	75.1	75.0
76																	76.9	76.7	76.6	76.4	76.3	76.2	76.1	76.0
77																	77.9	77.7	77.6	77.4	77.3	77.2	77.1	77.0
78																	78.9	78.7	78.6	78.4	78.3	78.2	78.1	78.0

TABLE IC. FOR ESTIMATING MATURE HEIGHT OF BOYS ACCELERATED MORE THAN ONE YEAR, BUT WITH SKELETAL AGES UNDER 13 YEARS

Skeletal Age	7-0	7-3	7-6	7-9	8-0	8-3	8-6	8-9	9-0	9-3	9-6	9-9	10-0	10-3	10-6	10-9	11-0	11-3	11-6	11-9	12-0	12-3	12-6
% of Mature Height	67.0	67.6	68.2	68.9	69.4	70.1	71.0	71.9	72.6	73.4	74.1	75.1	75.9	76.8	77.7	78.3	79.2	80.0	80.8	81.5	82.5	83.5	84.5
Ht. (inches)																							
43	64.2	63.6																					
44	65.7	65.1	64.5	63.9																			
45	67.2	66.6	66.0	65.3																			
46	68.7	68.0	67.4	66.8																			
47	70.1	69.5	68.9	68.2	67.7	67.0	66.2	65.4															
48	71.6	71.0	70.4	69.7	69.2	68.5	67.6	66.8	66.1	65.4	64.8												
49	73.1	72.5	71.8	71.1	70.6	69.9	69.0	68.2	67.5	66.8	66.1	65.2	64.6										
50	74.6	74.0	73.3	72.6	72.0	71.3	70.4	69.5	68.9	68.1	67.5	66.6	65.9	65.1	64.4	63.9							
51	76.1	75.4	74.8	74.0	73.5	72.8	71.8	70.9	70.2	69.5	68.8	67.9	67.2	66.4	65.6	65.1							
52	77.6	76.9	76.2	75.5	74.9	74.2	73.2	72.3	71.6	70.8	70.2	69.2	68.5	67.7	66.9	66.4	65.7	65.0	64.4	63.8			
53		78.4	77.7	76.9	76.4	75.6	74.6	73.7	73.0	72.2	71.5	70.6	69.8	69.0	68.2	67.7	66.9	66.2	65.0	65.0	64.2	63.5	62.7
54					77.8	77.0	76.1	75.1	74.4	73.6	72.9	71.9	71.1	70.3	69.5	69.0	68.2	67.5	66.8	66.3	65.5	64.7	63.9
55							77.5	76.5	75.8	74.9	74.2	73.2	72.5	71.6	70.9	70.2	69.4	68.8	68.1	67.5	66.7	65.9	65.1
56									77.1	76.3	75.6	74.6	73.8	72.9	72.1	71.5	70.7	70.0	69.3	68.7	67.9	67.1	66.3
57									78.5	77.7	76.9	75.9	75.1	74.2	73.4	72.8	72.0	71.2	70.5	69.9	69.1	68.3	67.5
58											78.3	77.2	76.4	75.5	74.6	74.1	73.2	72.5	71.8	71.2	70.3	69.5	68.6
59													77.7	76.8	75.9	75.3	74.5	73.8	73.0	72.4	71.5	70.7	69.8
60														78.1	77.2	76.6	75.8	75.0	74.3	73.6	72.7	71.9	71.0
61																	77.0	76.2	75.5	74.8	73.9	73.1	72.2
62																	78.3	77.5	76.7	76.1	75.2	74.3	73.4
63																			78.0	77.3	76.4	75.4	74.6
64																				78.5	77.6	76.6	75.7
65																							76.9

Note: If deviation in skeletal age is more than two years, estimate is height predicted from this table, "or taller."

TABLE ID. FOR ESTIMATING MATURE HEIGHT OF BOYS RETARDED MORE THAN ONE YEAR BUT WITH SKELETAL AGES UNDER 12

Skeletal Age	6-0	6-3	6-6	6-9	7-0	7-3	7-6	7-9	8-0	8-3	8-6	8-9	9-0	9-3	9-6	9-9	10-0	10-3	10-6	10-9	11-0	11-3	11-6	11-9
% of Mature Height	69.5	69.8	70.3	71.0	71.6	72.5	73.0	73.7	74.2	74.9	75.8	76.7	77.4	78.2	78.9	79.7	80.3	81.0	81.2	81.8	82.2	83.0	83.5	84.0
Ht. (inches)																								
43	61.9	61.6	61.2	60.6	60.0																			
44	63.3	63.0	62.6	62.0	61.4	60.7	60.3																	
45	64.7	64.5	64.0	63.4	62.8	62.1	61.6	61.0																
46	66.2	65.9	65.4	64.8	64.2	63.4	63.0	62.4	62:0	61.4	60.7	60.0												
47	67.6	67.3	66.9	66.2	65.6	64.8	64.4	63.8	63.3	62.8	62.0	61.3												
48	69.1	68.8	68.3	67.6	67.0	66.2	65.8	65.1	64.7	64.1	63.3	62.6	62.0	61.4	60.8	60.2								
49	70.5	70.2	69.7	69.0	68.4	67.6	67.1	66.5	66.0	65.4	64.6	63.9	63.3	62.7	62.1	61.5								
50	71.9	71.6	71.1	70.4	69.8	69.0	68.5	67.8	67.4	66.8	66.0	65.2	64.6	63.9	63.4	62.7	62.3	61.7	61.6	61.1				
51	73.4	73.1	72.5	71.8	71.2	70.3	69.9	69.2	68.7	68.1	67.3	66.5	65.9	65.2	64.6	64.0	63.5	63.0	62.8	62.3				
52					72.6	71.7	71.2	70.6	70.1	69.4	68.6	67.8	67.2	66.5	65.9	65.2	64.8	64.2	64.0	63.6	63.3	62.7	62.3	61.9
53					74.0	73.1	72.6	71.9	71.4	70.8	69.9	69.1	68.5	67.8	67.2	66.5	66.0	65.4	65.3	64.8	64.5	63.9	63.5	63.1
54								73.3	72.8	72.1	71.2	70.4	69.8	69.1	68.4	67.8	67.2	66.7	66.5	66.0	65.7	65.0	64.7	64.3
55									74.1	73.4	72.6	71.7	71.1	70.3	69.7	69.0	68.5	67.9	67.7	67.2	66.9	66.3	65.9	65.5
56											73.9	73.0	72.4	71.6	71.0	70.3	69.7	69.1	69.0	68.5	68.1	67.5	67.1	66.7
57													73.6	72.9	72.2	71.5	71.0	70.4	70.2	69.7	69.3	68.7	68.3	67.9
58															73.5	72.8	72.2	71.6	71.4	70.9	70.6	69.9	69.5	69.0
59																	73.5	72.8	72.7	72.1	71.8	71.1	70.7	70.2
60																		74.1	73.9	73.3	73.0	72.3	71.9	71.4
61																				74.6	74.2	73.5	73.1	72.6
62																					75.4	74.7	74.3	73.8
63																								75.0

Note: If deviation in skeletal age is more than two years, estimate is height predicted from this table, "or shorter."

TABLE IIA. FOR ESTIMATING MATURE HEIGHT OF GIRLS WITH SKELETAL AGES WITHIN ONE YEAR OF THEIR CHRONOLOGICAL AGES: SKELETAL AGES FROM 6 THROUGH 11 YEARS

Skeletal Age	6-0	6-3	6-6	6-9	7-0	7-3	7-6	7-9	8-0	8-3	8-6	8-9	9-0	9-3	9-6	9-9	10-0	10-3	10-6	10-9	11-0
% of Mature Height	72.0	72.2	72.7	73.4	74.1	75.0	76.1	76.7	77.5	78.2	79.0	79.8	81.0	81.3	82.2	83.1	84.0	84.9	85.6	86.2	87.2
Ht. (inches)																					
40	55.6	55.4	55.0	54.5																	
41	56.9	56.8	56.4	55.9																	
42	58.3	58.2	57.8	57.2																	
43	59.7	59.6	59.1	58.6	58.0	57.3	56.5														
44	61.1	60.9	60.5	59.9	59.4	58.7	57.8	57.4	56.8	56.3	55.7	55.1	54.3	54.1	53.5	52.9	52.4	51.8			
45	62.5	62.3	61.9	61.3	60.7	60.0	59.1	58.7	58.1	57.5	57.0	56.4	55.6	55.4	54.7	54.2	53.6	53.0	52.6	52.2	
46	63.9	63.7	63.3	62.7	62.1	61.3	60.4	60.0	59.4	58.8	58.2	57.6	56.8	56.6	56.0	55.4	54.8	54.2	53.7	53.4	52.8
47	65.3	65.1	64.6	64.0	63.4	62.7	61.8	61.3	60.6	60.1	59.5	58.9	58.0	57.8	57.2	56.6	56.0	55.4	54.9	54.5	53.9
48	66.7	66.5	66.0	65.4	64.8	64.0	63.1	62.6	61.9	61.4	60.8	60.2	59.3	59.0	58.4	57.8	57.1	56.5	56.1	55.7	55.0
49	68.1	67.9	67.4	66.8	66.1	65.3	64.4	63.9	63.2	62.7	62.0	61.4	60.5	60.3	59.6	59.0	58.3	57.7	57.2	56.8	56.2
50	69.4	69.3	68.8	68.1	67.5	66.7	65.7	65.2	64.5	63.9	63.3	62.7	61.7	61.5	60.8	60.2	59.5	58.9	58.4	58.0	57.3
51				69.5	68.8	68.0	67.0	66.5	65.8	65.2	64.6	63.9	63.0	62.7	62.0	61.4	60.7	60.1	59.6	59.2	58.5
52				70.8	70.2	69.3	68.3	67.8	67.1	66.5	65.8	65.2	64.2	64.0	63.3	62.6	61.9	61.2	60.7	60.3	59.6
53					71.5	70.7	69.6	69.1	68.4	67.8	67.1	66.4	65.4	65.2	64.5	63.8	63.1	62.4	61.9	61.5	60.8
54							71.0	70.4	69.7	69.1	68.4	67.7	66.7	66.4	65.7	65.0	64.3	63.6	63.1	62.6	61.9
55									71.0	70.3	69.6	68.9	67.9	67.7	66.9	66.2	65.5	64.8	64.3	63.8	63.1
56									72.3	71.6	70.9	70.2	69.1	68.9	68.1	67.4	66.7	66.0	65.4	65.0	64.2
57											72.2	71.4	70.4	70.1	69.3	68.6	67.9	67.1	66.6	66.1	65.4
58													71.6	71.3	70.6	69.8	69.0	68.3	67.8	67.3	66.5
59														72.6	71.8	71.0	70.2	69.5	68.9	68.4	67.7
60																72.2	71.4	70.7	70.1	69.6	68.8
61																	72.6	71.8	71.3	70.8	70.0
62																			72.4	71.9	71.1
63																				73.1	72.2

TABLE IIB. FOR ESTIMATING MATURE HEIGHT OF GIRLS WITH SKELETAL AGES BETWEEN 11 YEARS AND MATURITY

Skeletal Age	11-3	11-6	11-9	12-0	12-3	12-6	12-9	13-0	13-3	13-6	13-9	14-0	14-3	14-6	14-9	15-0	15-3	15-6	15-9	16-0	16-3	16-6
% of Mature Height	88.0	89.2	90.3	91.7	92.7	93.6	94.7	95.5	96.5	97.2	97.7	98.0	98.5	98.6	98.9	99.0	99.1	99.4	99.6	99.8	99.9	100
Ht. (inches)																						
46	52.3																					
47	53.4	52.7	52.0																			
48	54.5	53.8	53.2	52.3	51.8																	
49	55.7	54.9	54.3	53.4	52.9	52.4	51.7															
50	56.8	56.0	55.4	54.5	53.9	53.4	52.8															
51	58.0	57.2	56.5	55.6	55.0	54.5	53.9	53.4	52.8	52.5	52.2											
52	59.1	58.3	57.6	56.7	56.1	55.6	54.9	54.4	53.9	53.5	53.2											
53	60.2	59.4	58.7	57.8	57.2	56.6	56.0	55.5	54.9	54.5	54.2	54.1	53.8	53.8								
54	61.4	60.5	59.8	58.9	58.3	57.7	57.0	56.5	56.0	55.6	55.3	55.1	54.8	54.8								
55	62.5	61.7	60.9	60.0	59.3	58.8	58.1	57.6	57.0	56.6	56.3	56.1	55.8	55.8	55.6	55.6	55.5	55.3				
56	63.6	62.8	62.0	61.1	60.4	59.8	59.1	58.6	58.0	57.6	57.3	57.1	56.9	56.8	56.6	56.6	56.5	56.3	56.2	56.1	56.1	56.0
57	64.8	63.9	63.1	62.2	61.5	60.9	60.2	59.7	59.1	58.6	58.3	58.2	57.9	57.8	57.6	57.6	57.5	57.3	57.2	57.1	57.1	57.0
58	65.9	65.0	64.2	63.2	62.6	62.0	61.2	60.7	60.1	59.7	59.4	59.2	58.9	58.8	58.6	58.6	58.5	58.4	58.2	58.1	58.1	58.0
59	67.0	66.1	65.3	64.3	63.6	63.0	62.3	61.8	61.1	60.7	60.4	60.2	59.9	59.8	59.7	59.6	59.5	59.4	59.2	59.1	59.1	59.0
60	68.2	67.3	66.4	65.4	64.7	64.1	63.4	62.8	62.2	61.7	61.4	61.2	60.9	60.9	60.7	60.6	60.5	60.4	60.2	60.1	60.1	60.0
61	69.3	68.4	67.6	66.5	65.8	65.2	64.4	63.9	63.2	62.8	62.4	62.2	61.9	61.9	61.7	61.6	61.6	61.4	61.2	61.1	61.1	61.0
62	70.5	69.5	68.7	67.6	66.9	66.2	65.5	64.9	64.3	63.8	63.5	63.3	62.9	62.9	62.7	62.6	62.6	62.4	62.2	62.1	62.1	62.0
63	71.6	70.6	69.8	68.7	68.0	67.3	66.5	66.0	65.3	64.8	64.5	64.3	64.0	63.9	63.7	63.6	63.6	63.4	63.3	63.1	63.1	63.0
64		71.7	70.9	69.8	69.0	68.4	67.6	67.0	66.3	65.8	65.5	65.3	65.0	64.9	64.7	64.6	64.6	64.4	64.3	64.1	64.1	64.0
65				70.9	70.1	69.4	68.6	68.1	67.4	66.9	66.5	66.3	66.0	65.9	65.7	65.7	65.6	65.4	65.3	65.1	65.1	65.0
66						70.5	69.7	69.1	68.4	67.9	67.6	67.3	67.0	66.9	66.7	66.7	66.6	66.4	66.3	66.1	66.1	66.0
67						71.6	70.7	70.2	69.4	68.9	68.6	68.4	68.0	68.0	67.7	67.7	67.6	67.4	67.3	67.1	67.1	67.0
68								71.2	70.5	70.0	69.6	69.4	69.0	69.0	68.8	68.7	68.6	68.4	68.3	68.1	68.1	68.0
69								72.3	71.5	71.0	70.6	70.4	70.1	70.0	69.8	69.7	69.6	69.4	69.3	69.1	69.1	69.0
70											71.6	71.4	71.1	71.0	70.8	70.7	70.6	70.4	70.3	70.1	70.1	70.0
71											72.7	72.4	72.1	72.0	71.8	71.7	71.6	71.4	71.3	71.1	71.1	71.0
72											73.7	73.5	73.1	73.0	72.8	72.7	72.7	72.4	72.3	72.1	72.1	72.0

TABLE IIC. FOR ESTIMATING MATURE HEIGHT OF GIRLS ACCELERATED MORE THAN ONE YEAR, BUT WITH SKELETAL AGES OF 14 YEARS OR LESS

Skeletal Age	7-0	7-3	7-6	7-9	8-0	8-3	8-6	8-9	9-0	9-3	9-6	9-9	10-0	10-3	10-6	10-9	11-0	11-3	11-6	11-9	12-0	12-3	12-6	12-9	13-0	13-3	13-6	13-9	14-0
% of Mature Height	71.6	72.8	73.7	74.6	75.4	76.1	77.0	77.9	78.6	79.3	80.3	81.0	82.0	82.8	83.6	84.6	85.3	86.5	87.3	88.5	89.8	90.8	91.8	93.1	94.1	95.5	96.3	97.0	97.5
Ht. (inches)																													
43	60.1	59.1	58.3																										
44	61.5	60.4	59.7	59.0	58.4	57.8	57.1	56.5	56.0	55.5	54.8	54.3	53.7	53.1															
45	62.8	61.8	61.1	60.3	59.7	59.1	58.4	57.8	57.3	56.7	56.0	55.6	54.9	54.3	53.8	53.2													
46	64.2	63.2	62.4	61.7	61.0	60.4	59.7	59.0	58.5	58.0	57.3	56.8	56.1	55.6	55.0	54.4	53.9	53.2											
47	65.6	64.6	63.8	63.0	62.3	61.8	61.0	60.3	59.8	59.3	58.5	58.0	57.3	56.8	56.2	55.6	55.1	54.3	53.8	53.1									
48	67.0	65.9	65.1	64.3	63.7	63.1	62.3	61.6	61.1	60.5	59.8	59.3	58.5	58.0	57.4	56.7	56.3	55.5	55.0	54.2	53.5	52.9	52.3						
49	68.4	67.3	66.5	65.7	65.0	64.4	63.6	62.9	62.3	61.8	61.0	60.5	59.8	59.2	58.6	57.9	57.4	56.6	56.1	55.4	54.6	54.0	53.4	52.6					
50	69.8	68.7	67.8	67.0	66.3	65.7	64.9	64.2	63.6	63.1	62.3	61.7	61.0	60.4	59.8	59.1	58.6	57.8	57.3	56.5	55.7	55.1	54.5	53.7					
51	71.2	70.1	69.2	68.4	67.6	67.0	66.2	65.5	64.9	64.3	63.5	63.0	62.2	61.6	61.0	60.3	59.8	59.0	58.4	57.6	56.8	56.2	55.6	54.8	54.2	53.4	53.0	52.6	52.3
52	72.6	71.4	70.6	69.7	69.0	68.3	67.5	66.8	66.2	65.6	64.8	64.2	63.4	62.8	62.2	61.5	61.0	60.1	59.6	58.8	57.9	57.3	56.6	55.9	55.3	54.4	54.0	53.6	53.3
53			71.9	71.0	70.3	69.6	68.8	68.0	67.4	66.8	66.0	65.4	64.6	64.0	63.4	62.6	62.1	61.3	60.7	59.9	59.0	58.4	57.7	56.9	56.3	55.5	55.0	54.6	54.4
54				72.4	71.6	71.0	70.1	69.3	68.7	68.1	67.2	66.7	65.9	65.2	64.6	63.8	63.3	62.4	61.9	61.0	60.1	59.5	58.8	58.0	57.4	56.5	56.1	55.7	55.4
55						72.3	71.4	70.6	70.0	69.4	68.5	67.9	67.1	66.4	65.8	65.0	64.5	63.6	63.0	62.1	61.2	60.6	59.9	59.1	58.4	57.6	57.1	56.7	56.4
56								71.9	71.2	70.6	69.7	69.1	68.3	67.6	67.0	66.2	65.7	64.7	64.1	63.3	62.4	61.7	61.0	60.2	59.5	58.6	58.2	57.7	57.4
57										71.9	71.0	70.4	69.5	68.8	68.2	67.4	66.8	65.9	65.3	64.4	63.5	62.8	62.1	61.2	60.6	59.7	59.2	58.8	58.5
58											72.2	71.6	70.7	70.0	69.4	68.6	68.0	67.1	66.4	65.5	64.6	63.9	63.2	62.3	61.6	60.7	60.2	59.8	59.5
59													72.0	71.3	70.6	69.7	69.2	68.2	67.6	66.7	65.7	65.0	64.3	63.4	62.7	61.8	61.3	60.8	60.5
60															71.8	70.9	70.3	69.4	68.7	67.8	66.8	66.1	65.4	64.4	63.8	62.8	62.3	61.9	61.5
61																72.1	71.5	70.5	69.9	68.9	67.9	67.2	66.4	65.5	64.8	63.9	63.3	62.9	62.6
62																	72.7	71.7	71.0	70.1	69.0	68.3	67.5	66.6	65.9	64.9	64.4	63.9	63.6
63																		72.8	72.2	71.2	70.2	69.4	68.6	67.7	67.0	66.0	65.4	64.9	64.6
64																				72.3	71.3	70.5	69.7	68.7	68.0	67.0	66.5	66.0	65.6
65																						71.6	70.8	69.8	69.1	68.1	67.5	67.0	66.7
66																							71.9	70.9	70.1	69.1	68.5	68.0	67.7
67																								72.0	71.2	70.2	69.6	69.1	68.7
68																									72.3	71.2	70.6	70.1	69.7

TABLE IID. FOR ESTIMATING MATURE HEIGHT OF GIRLS RETARDED MORE THAN ONE YEAR, BUT WITH SKELETAL AGES UNDER 12 YEARS

Skeletal Age	6-0	6-3	6-6	6-9	7-0	7-3	7-6	7-9	8-0	8-3	8-6	8-9	9-0	9-3	9-6	9-9	10-0	10-3	10-6	10-9	11-0	11-3	11-6	11-9
% of Mature Height	74.2	74.5	75.0	75.7	76.5	77.4	78.0	78.7	79.8	80.5	81.3	82.0	82.8	83.8	84.5	85.2	86.1	86.8	87.6	88.0	88.2	89.0	90.0	91.0
Ht. (inches)																								
40	53.9	53.7	53.3	52.8																				
41	55.3	55.0	54.7	54.2																				
42	56.6	56.4	56.0	55.5																				
43	58.0	57.7	57.3	56.8	56.2	55.6	55.1																	
44	59.3	59.1	58.7	58.1	57.5	56.8	56.4	55.9	55.1	54.7	54.1	53.7	53.1	52.5	52.1	51.6	51.1	50.7						
45	60.6	60.4	60.0	59.4	58.8	58.1	57.7	57.2	56.4	55.9	55.4	54.9	54.3	53.7	53.2	52.8	52.3	51.8	51.4	51.1				
46	62.0	61.7	61.3	60.7	60.1	59.4	59.0	58.4	57.6	57.1	56.6	56.1	55.6	54.9	54.4	54.0	53.4	53.0	52.5	52.3	52.2	51.7		
47	63.3	63.1	62.7	62.1	61.4	60.7	60.3	59.7	58.9	58.4	57.8	57.3	56.8	56.1	55.6	55.2	54.6	54.1	53.7	53.4	53.3	52.8	52.2	51.6
48	64.5	64.4	64.0	63.4	62.7	62.0	61.5	61.0	60.2	59.6	59.0	58.5	58.0	57.3	56.8	56.3	55.7	55.3	54.8	54.5	54.4	53.9	53.3	52.7
49	66.0	65.8	65.3	64.7	64.1	63.3	62.8	62.3	61.4	60.9	60.3	59.8	59.2	58.5	58.0	57.5	56.9	56.5	55.9	55.7	55.6	55.1	54.4	53.8
50	67.4	67.1	66.7	66.1	65.4	64.6	64.1	63.5	62.7	62.1	61.5	61.0	60.4	59.7	59.2	58.7	58.1	57.6	57.1	56.8	56.7	56.2	55.6	54.9
51				67.4	66.7	65.9	65.4	64.8	63.9	63.4	62.7	62.2	61.6	60.9	60.4	59.9	59.2	58.8	58.2	58.0	57.8	57.3	56.7	56.0
52				68.7	68.0	67.2	66.7	66.1	65.2	64.6	64.0	63.4	62.8	62.1	61.5	61.0	60.4	59.9	59.4	59.1	59.0	58.4	57.8	57.1
53					69.3	68.5	67.9	67.3	66.4	65.8	65.2	64.6	64.0	63.2	62.7	62.2	61.6	61.1	60.5	60.2	60.1	59.6	58.9	58.2
54							69.2	68.6	67.7	67.1	66.4	65.9	65.2	64.4	63.9	63.4	62.7	62.2	61.6	61.4	61.2	60.7	60.0	59.3
55									68.9	68.3	67.7	67.1	66.4	65.6	65.1	64.6	63.9	63.4	62.8	62.5	62.4	61.8	61.1	60.4
56										69.6	68.9	68.3	67.6	66.8	66.3	65.7	65.0	64.5	63.9	63.6	63.5	62.9	62.2	61.5
57											70.1	69.5	68.8	68.0	67.5	66.9	66.2	65.7	65.1	64.8	64.6	64.0	63.3	62.6
58													70.0	69.2	68.6	68.1	67.4	66.8	66.2	65.9	65.8	65.2	64.4	63.7
59														70.4	69.8	69.2	68.5	68.0	67.4	67.0	66.9	66.3	65.6	64.8
60																	69.6	69.1	68.5	68.2	68.0	67.4	66.7	65.9
61																	70.8	70.3	69.6	69.3	69.2	68.5	67.8	67.0
62																			70.8	70.5	70.3	69.7	68.9	68.1
63																						70.8	70.0	69.2
64																							71.1	70.3

Note: If deviation in skeletal age is more than two years, estimate is height predicted from this table, "or shorter."

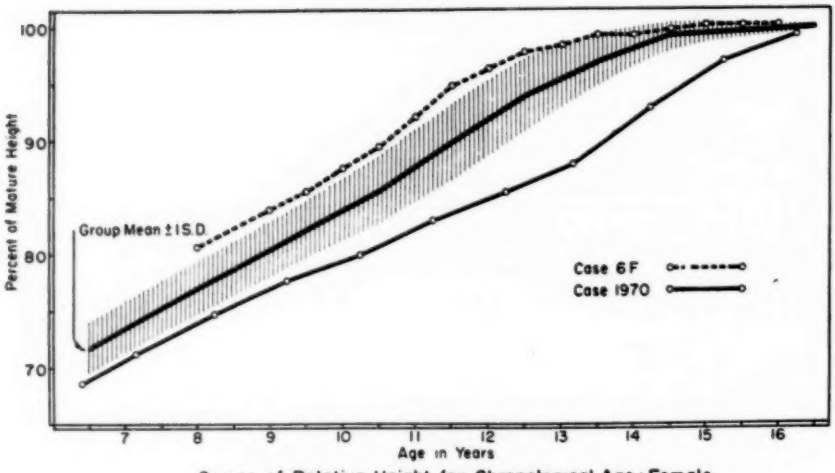


Fig. 1.—Curve of the average per cent of their own mature height achieved, at successive chronological ages, by 100 girls. Shown in comparison are two individual cases, a fast-maturing girl (No. 6F), and a slow-maturing girl (No. 1970).

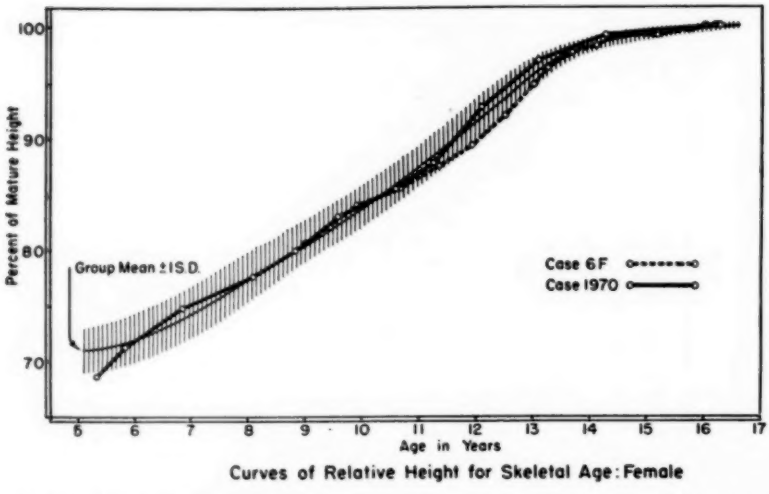


Fig. 2.—Curve of the average per cent of their own mature height achieved, at successive skeletal ages, by 100 girls. Shown also are the curves of the relative heights of the same slow-maturing and fast-maturing girls as shown in Fig. 1 (No. 6F and No. 1970), plotted against their skeletal ages.

ACCURACY OF PREDICTION

The degree of accuracy of prediction is indicated in Tables V and VI. Individual children's heights were predicted in two ways: they were read from the tables on the basis of skeletal age by the method described, and they were also predicted from chronological age alone, using Tables IA and IB and IIA and IIB, as though they were chronological age tables. By computing the differences between actual mature height and these predicted heights, the error of prediction was determined for two groups of children at successive ages. These groups are (1) twenty Berkeley girls[5] who were not included in the construction of the tables, and (2) the Harvard Growth Study boys (there were no data available on fully mature boys not used in developing the prediction tables;

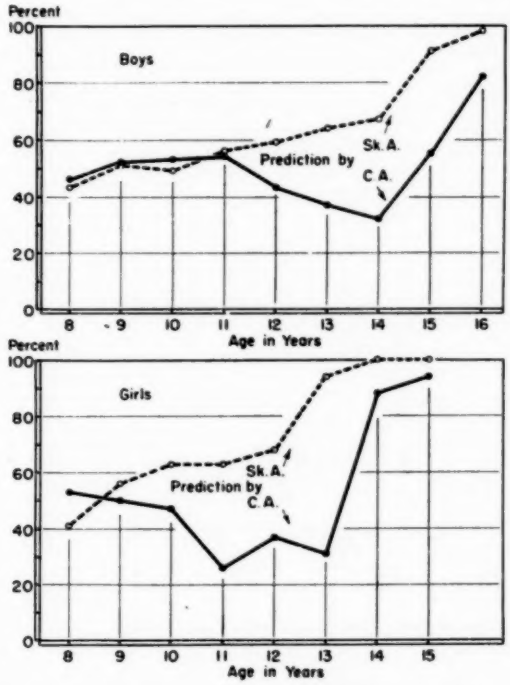


Fig. 3.—The per cent of cases for whom prediction was within one inch of actual final height; *A*, 100 Massachusetts boys; *B*, 20 California girls.

ideally it is preferable to test the usefulness of the tables on cases not used in their construction). The average error of prediction is smaller when prediction is made from skeletal ages than when made from chronological ages only. This is shown both by the means of the prediction errors, and by their standard deviations, which show a clustering of predictions much closer to the true height when skeletal age is made the basis of prediction. The relative accuracy of predic-

tion from skeletal age, as compared with chronological age, is shown in another way in Fig. 3, which shows for ages 8 to 16 the per cent of cases for whom the prediction is accurate to an inch or better. Examples of the error of prediction in individual cases are shown for the two deviate girls (Case 6F and Case 1970) in Tables III and IV, respectively. Again we see that the use of skeletal ages greatly increases the accuracy of prediction.*

It must be kept in mind, however, that for the younger ages the error is often as much as an inch or even more. The greatest value to be gained from

TABLE III. A GIRL WHO IS ACCELERATED IN SKELETAL DEVELOPMENT
Case 6F—Mature Height = 65.4 Inches

C.A. YR.-MO.	SK.A. YR.-MO.	HEIGHT (INCHES)	PER CENT MATURE HEIGHT	PREDICTED HEIGHT FROM C.A. (INCHES)	ERROR OF C.A. PREDICTIONS (INCHES)	PREDICTED HEIGHT FROM SK.A. (INCHES)	ERROR OF SK.A. PREDICTIONS (INCHES)
8-0	9-0	52.7	80.6	68.0	+2.5	65.0	-0.4
9-0	9-11	54.9	83.9	67.8	+2.3	65.6	+0.2
9-6	10-8	55.9	85.5	68.0	+2.5	66.4	+1.0
10-0	11-4	57.2	87.5	68.1	+2.6	65.9	+0.5
10-6	11-11	58.5	89.4	68.4	+2.9	65.5	+0.1
11-0	12-6	60.2	92.0	69.0	+3.5	65.6	+0.2
11-6	13-0	62.0	94.8	69.5	+4.0	65.9	+0.5
12-0	13-3	63.0	96.3	68.7	+3.2	66.0	+0.6
12-6	13-8	63.9	97.7	68.3	+2.8	66.1	+0.7
13-0	14-1	64.3	98.3	67.3	+1.8	65.7	+0.3
13-6	14-5	64.9	99.2	66.8	+1.3	65.8	+0.4
14-0	15-2	64.9	99.2	66.2	+0.7	65.5	+0.1
14-6	15-9	65.2	99.7	66.1	+0.6	65.5	+0.1
15-0	16-0	65.4	100.0	66.1	+0.6	65.5	+0.1
15-6	16-2	65.4	100.0	65.8	+0.3	65.5	+0.1
16-0	16-3	65.4	100.0	65.5	+0.1	65.4	+0.0
				Mean error = +1.98		Mean error = +0.30	

TABLE IV. A GIRL WHO IS RETARDED IN SKELETAL DEVELOPMENT
Case 1970—Mature Height = 62.2 Inches

C.A. YR.-MO.	SK.A. YR.-MO.	HEIGHT (INCHES)	PER CENT MATURE HEIGHT	PREDICTED HEIGHT FROM C.A. (INCHES)	ERROR OF C.A. PREDICTIONS (INCHES)	PREDICTED HEIGHT FROM SK.A. (INCHES)	ERROR OF SK.A. PREDICTIONS (INCHES)
6-5	5-4	42.6	68.6	58.6	-3.6	59.6	-2.6
7-2	5-10	44.3	71.2	59.3	-2.9	60.0	-2.2
8-3	6-10	46.5	74.7	59.4	-2.8	61.2	-1.0
9-3	8-1	48.2	77.6	60.1	-2.1	60.2	-2.0
10-3	8-10	49.7	79.9	58.5	-3.7	60.4	-1.8
11-3	9-7	51.6	82.9	58.7	-3.5	61.0	-1.2
12-3	10-7	53.1	85.4	57.3	-4.9	60.5	-1.7
13-2	11-3	54.5	87.8	56.6	-5.6	61.3	-0.9
14-3	12-1	57.7	92.8	58.6	-3.6	62.7	+0.5
15-3	13-1	60.2	96.9	60.7	-1.5	62.9	+0.7
16-3	14-3	61.7	99.2	61.8	-0.4	62.6	+0.4
17-3	16-3	62.2	100.0	62.2	0.0	62.3	+0.1
				Mean Error = -2.88		Mean Error = -0.98	

*Skeletal Ages for the Berkeley Growth Study cases are averages of hand and knee assessments, while the Harvard Growth Study skeletal ages were read from x-rays of a part of the hand only. This may account for the greater accuracy of prediction from skeletal age of Case 6F as compared with Case 1970, as well as for the Berkeley girls as compared with the Harvard boys (Tables V and VI).

TABLE V. ERROR IN HEIGHT PREDICTION BY CHRONOLOGICAL AGE AND SKELETAL AGE—BERKELEY GROWTH STUDY (GIRLS)

AGE IN YEARS AND MONTHS	PREDICTION BY C.A.			PREDICTION BY SK.A.	
	N	MEAN ERROR (INCHES)	S.D.	MEAN ERROR (INCHES)	S.D.
8-0	17	+ .15	1.55	-.76	1.44
9-0	18	+ .05	1.57	-.09	1.64
9-6	18	+ .71	1.74	+.13	1.50
10-0	19	+ .67	1.85	-.34	1.29
10-6	19	+ .93	2.09	-.62	1.01
11-0	19	+1.06	2.05	-.69	.88
11-6	19	+1.30	2.35	-.61	1.02
12-0	19	+1.01	2.20	-.27	.94
12-6	19	+ .88	1.89	-.23	.60
13-0	16	+ .44	1.54	-.03	.55
13-6	16	+ .06	1.30	+.08	.38
14-0	17	+ .26	.93	+.21	.38
14-6	17	+ .21	.67	+.09	.32
15-0	17	+ .29	.49	+.11	.18
15-6	19	+ .21	.33	+.05	.11
16-0	17	- .06	.24	-.05	.15

TABLE VI. ERROR IN HEIGHT PREDICTION BY CHRONOLOGICAL AGE AND SKELETAL AGE—HARVARD GROWTH STUDY (BOYS)

AGE IN YEARS AND MONTHS (MIDPOINT)	PREDICTION BY C.A.			PREDICTION BY SK.A.		
	N	MEAN ERROR (INCHES)	S.D.	N	MEAN ERROR (INCHES)	S.D.
7-6	102	-.61	1.76	96	-.23	1.73
8-6	97	+.07	1.65	96	+.21	1.60
9-6	103	-.004	1.66	103	+.30	1.48
10-6	98	-.04	1.64	97	+.21	1.39
11-6	102	+.08	1.94	98	+.04	1.35
12-6	100	+.49	2.59	97	+.07	1.26
13-6	102	+.46	2.85	100	+.20	1.11
14-6	99	+.33	2.38	96	+.32	1.00
15-6	98	+.31	1.45	97	+.28	.60
16-6	96	+.35	.69	96	+.20	.39
17-6	91	+.27	.31	91	+.10	.22

the skeletal age tables is for the period during which adolescent growth spurts occur—that is, after 10 years for girls, and 12 years for boys.

DISCUSSION

Two other recent studies, besides the one on which this report is based, have reported similar relationships between growth in size and developmental changes in the skeleton. Simmons,[6] working on the Brush Foundation material from which the Todd standards were developed, reports findings closely similar to those found for the children in the California Adolescent Growth Study.[1] Simmons' data as well as ours show that skeletal age is much more highly correlated with relative size than is chronological age. She also calls attention to the possibility of predicting adult height on the basis of skeletal age. But she does not give specific methods for computing the predictions.

Gill and Abbott[7] have devised a method for predicting height, in order to predict growth of the femur and tibia. Their purpose is a practical one—to de-

termine the amount of change to make in osteotomy for equalizing leg lengths. They use published data on percentile groups of heights at successive ages, and predict from skeletal age, disregarding chronological age, if a child is retarded or accelerated more than six months in skeletal age. Our method appears to be more accurate than theirs because of refinements made possible by the nature of the data avaliable to us. It should prove of value for the same purposes.

Shuttleworth[8] has developed tables for predicting mature height, using other criteria of physical maturity, primarily the age at maximum growth. His main tables, for prediction from a given initial height and age, are intended for children maturing at the average rate. To correct for deviations in velocities of maturing he gives a series of supplementary tables which can be used only if a child has been measured at least twice with *exactly* one year intervening between measurings. The prediction is then determined from height, age, and the annual increment in stature since the previous measure. This procedure is very cumbersome and requires an exactitude of measures and intervals which are rarely available clinically. However, when correctly determined (and when increments can be correctly located in relation to age at maximum growth) predictions may yield results similar to ours, because both systems have grown out of similar premises concerning characteristic growth trends of children with differing velocities of physical maturing.

It is hoped that the tables presented here will have clinical usefulness. They should prove of value, when used with x-rays of the hand and/or other ossification centers which have been assigned skeletal ages, in predicting the adult height of children whose growth is incomplete. It seems very likely that further knowledge of the factors influencing growth will eventually make it possible to predict height with even greater accuracy than the use of skeletal-age-height tables permit.

REFERENCES

1. Bayley, N.: Child Development **14**: 1, 1943.
2. Bayley, N.: Child Development **14**: 47, 1943.
3. Todd, T. W.: Atlas of Skeletal Maturation (Hand), St. Louis, 1937, The C. V. Mosby Company, p. 303; Also Child Development **1**: 298, 1930.
4. Flory, D. C.: Monographs of the Society for Research in Child Development, 1936, vol. 1, p. 141.
5. Bayley, N., and Jones, H. E.: Child Development **12**: 167, 1941.
6. Simmons, K.: Monographs of the Society for Research in Child Development, 1944, vol. 9, p. 104.
7. Gill, G. G., and Abbott, L. C.: Arch. Surg. **45**: 286, 1942.
8. Shuttleworth, F. K.: Monographs of the Society for Research in Child Development **4**: 291, 1939.

THE USE OF PROSTIGMINE IN THE MANAGEMENT OF INFANTILE CEREBRAL PARALYSIS

PAUL N. JEPSON, M.D., M.S.
PHILADELPHIA, PA.

IN SPITE of much study and innumerable special investigation as to the causative factors and pathology of infantile cerebral paralysis (variously known as spastic paralysis, Little's disease, or cerebral diplegia), at present there is little unanimity of opinion. Even less agreement exists as to the preferred method of treatment.

The most widely prevalent theory as to the etiology of this condition is that it is necessarily caused by birth trauma or obstetric mismanagement. Recently, however, Heyman[1] reviewed the literature on this subject and came to the conclusion that there are many factors which give rise to the clinical entity known as spastic paralysis. Among these he listed neuropathic heredity, primary degeneration of the brain or developmental arrest, infections, premature birth, hemorrhagic disease of the newborn, asphyxia, and anoxemia.

The traumatic factor, whether or not it is the most important one, has in any case received the most attention. It is commonly believed that a difficult and prolonged labor or an instrumental or breech delivery may result in intracranial hemorrhage. Such bleeding is due to a laceration of the dura mater or possibly in the brain substance itself. In some instances the lesion may be more widespread as a result of a temporary obstruction of the circulation. Degeneration of the nervous tissue followed by sclerosis may result in foci of atrophy and softening. Similar changes can and do occur in the spinal cord, especially when there has been traction on the neck during delivery.

The clinical classification is as difficult as the etiologic and pathologic.[2] The spastic diplegias are usually not manifest for the first few months of life. However, there may be some early spasticity or the infant's limbs may be closely adducted. These signs become more evident as the child learns to walk, a function which is often delayed till the age of 2, 3, or even 4 years. The gait is usually spastic and commonly known as "scissors gait." If the lesion is confined to the upper motor cortex, the spastic paralysis is limited to the lower extremities.

Even in the mildest cases there is definite evidence of involvement of the pyramidal tract in the form of increased deep tendon reflexes. It follows that there is considerable muscular weakness or even paralysis. No sensory disturbances are usually seen.

Other signs of cerebral involvement are generally present. Various grades of mental impairment are common, ranging from irritability and hyperexcitability to imbecility or idiocy.[2] True epileptic convulsions are suffered by some patients. The speech is likely to be impaired, perhaps due to spasticity of the muscles used in articulation. It is believed that not infrequently the mental retardation may be due at least in part to discouragement of education of the

child because of his physical impairment. In this respect a very careful history is essential. Painstaking observation over a period of several months may often determine whether or not the condition is progressive, and whether or not there is true mental retardation.

TREATMENT

The treatment of infantile cerebral paralysis has been considered highly unsatisfactory. The essential principle involved is one of training and rehabilitation over a prolonged period. Some clinicians advocate operative intervention as an adjunct to the re-education program. For example, the Foerster operation of cutting certain sensory roots to overcome the spasticity has been reported to have produced good results in some cases. A similar procedure on the motor nerves (Stoffel operation) is designed to bring about the same effect. However, all such operative procedures have the disadvantage of permanently interrupting nerve pathways and of inducing physiologic changes which are undesirable.

More hope can be expected from physiotherapeutic measures such as massage, baking, active and passive motion, and coordinating exercises. Persistent re-educational measures are the sheet anchor of therapy. Recently a drug has been added to our therapeutic armamentarium which aids materially by decreasing or abolishing muscle spasticity, thus helping the patient to relax sufficiently to allow slow, controlled movement of the extremities. The drug chosen is prostigmine.

Prostigmine is a parasympathetic stimulant which has recently been shown to have a depressant action on the spinal cord. Deep reflexes can be abolished and muscle spasticity appreciably lessened by the administration of prostigmine in man.[3-7]

Accordingly, in 1943, we began to use prostigmine bromide by mouth in an attempt to reduce the muscle spasticity in our patients. Cases at first were chosen at random, regardless of age or chronicity. However, it was soon discovered that the younger the patient was at the beginning of therapy, the more likely was prostigmine to afford beneficial results. Since starting this work Kabat[8] as well as Schaubel[9] have reported very favorable results in similar cases with prostigmine therapy.

The dosage was governed by the age of the patient, but the minimum dose in all cases regardless of age was 5 mg. of prostigmine bromide (one-third of a standard 15 mg. tablet). When first administered the patient was instructed to take the minimum dose (5 mg.) by mouth three times per day. After a period of two weeks, provided no adverse reaction was observed, the dose was given four or more times per day. Strangely enough, single doses larger than 5 mg. proved less beneficial and more likely to cause diarrhea and abdominal cramps, especially in small children.

It was found in the cases observed and treated that in children under the age of 12 years there was a definite lessening of spasticity and an increase in the function of the muscles involved. Results were often noted as early as 2

or 3 weeks after the beginning of treatment. However, it was quite evident that prostigmine medication must be continued for at least six months, or until further improvement was no longer noted. It was found that if the drug was discontinued at the end of two or three months there was a partial recurrence of the former spastic symptoms. On the contrary, if medication was continued regularly and persistently (from four to eight times daily) for six months there seemed to develop an habitual improvement even after treatment was discontinued. As a matter of fact, during this period the patient apparently "learned" how to relax.

No such beneficial results were observed in the two adult cases so treated (aged 32 and 34, respectively). Although prostigmine appeared to afford some relaxation, there was not sufficient depression of the spasticity to enable the patient to relax voluntarily in order to respond to muscle re-education and training.

To date, some twenty-five patients have been subjected to prostigmine therapy, the great majority of them being between the ages of 2 and 6 years. In general the results have been most encouraging. It is to be emphasized that the usually accepted, standard forms of therapy, including physiotherapeutic measures and re-education must be employed concomitantly with prostigmine medication if the most favorable results are to be obtained. Such measures usually can be efficiently carried out by the child's mother and the patient's general condition and progress checked by the attending physician every two weeks. Furthermore, it is believed that frequent small doses of prostigmine bromide by mouth, administered throughout the waking hours, afford a more continuous decrease of muscle spasm than do larger doses given less often.

SUMMARY

Although it must be acknowledged that this is a small series of cases upon which to base any definite conclusion, it is thought that there is sufficient evidence to warrant the continued use of prostigmine as suggested and eventually to be able to compile end results from numerous investigators and draw conclusions that may be standardized, thereby obtaining some benefit for a condition that up to now has been most discouraging to both patient and physician. This preliminary report is published in the hope of stimulating further study and research in the adjunctive use of prostigmine in the management of children with infantile cerebral paralysis.

REPRESENTATIVE CASE REPORTS

CASE 1.—J. B., a 2½-year-old white boy, was first seen in the clinic on Nov. 11, 1942. The father gave a history that the child had had symptoms of a spastic cerebral paralysis since birth, and that the only previous therapy had been the use of special corrective shoes.

Examination revealed marked spasticity of the right upper extremity. The right Achilles tendon was quite taut, and only when the child's attention was distracted could the foot be brought into a neutral position. The upper extremity was almost functionless.

The parents were given instructions as to massage and exercises of the right upper extremity. In addition the right Achilles tendon was lengthened by surgery.

He was seen in February, 1943, at which time walking was quite satisfactory although the right Achilles tendon still was quite taut. In June, 1943, a splint was applied to the left hand in order to hold the thumb and other fingers in the extended position.

Prostigmine therapy was instituted in Sept., 1943, 4 mg. (prepared in capsule form) being given three times per day. Gradual, increasing improvement was noted during the next seven months during which time the prostigmine was increased to 5 mg. given six times per day. When last seen in October, 1944, the child could walk quite well, could throw a ball, and was generally improved to a considerable degree. (Prostigmine therapy had been started again in July, 1944).

CASE 2.—T. T., a 2½-year-old white boy, was first seen by us in October, 1944. Although the chief complaint was flat feet, examination revealed sufficient spasticity of the left lower extremity to justify a diagnosis of spastic cerebral paralysis.

Treatment at first consisted only of the wearing of special corrective shoes having "pigeon toe" wedges. When seen one month later, at which time the spasticity was pronounced, 5 mg. of prostigmine bromide was prescribed three times per day and coordinating exercises were demonstrated. Three weeks later there was an appreciable decrease in spasticity of the left lower extremity. Prostigmine dosage was gradually increased until 30 mg. daily was given in divided doses. When last seen in March, 1945, (four months after the initiation of prostigmine therapy) the child was greatly improved, and walking was almost normal.

Most of the other cases follow a similar pattern and have for this reason not been recorded.

REFERENCES

1. Heyman, C. H.: J. A. M. A. **111**: 493, 1938.
2. Wechsler, I. S.: A Textbook of Clinical Neurology, ed. 5, revised, Philadelphia and London, 1943, W. B. Saunders Company.
3. Kremer, Michael: Quart. J. Physiol. **31**: 337, 1942.
4. Kabat, H., and Knapp, M. E.: J. A. M. A. **122**: 989, 1943.
5. Wolf, A.: J. Nerv. and Ment. Dis. **92**: 614, 1940.
6. Trommer, P. R., and Cohen, A.: J. A. M. A. **124**: 1237, 1944.
7. Kabat, H., and Knapp, M. E.: J. PEDIAT. **24**: 123, 1944.
8. Kabat, H.: Pub. Health Rep. **59**: 1635, 1944.
9. Schaubel, H. J.: Physiotherapy Rev. **24**: 236, 1944.

CORD TRANSFUSIONS IN NEWBORN INFANTS

A Report of Ninety-Nine Cord Transfusions in Premature Babies, Twenty-One in Full-Term Babies and Seventy-Eight in Babies of Rh-Negative Mothers

Harry W. Mayes, A.M., M.D., F.A.C.S.
Brooklyn, N. Y.

FOLLOWING a long labor, difficult forceps delivery, or breech extraction, the infants are frequently in severe shock. Not infrequently they are suffering from hemorrhage, which may not always be apparent at birth but develops shortly after. In premature babies the blood has a low content of vitamin K and prothrombin, and premature infants are much more subject to hemorrhage and will not withstand as much trauma as full-term infants. Taking these facts into consideration, it would seem that if newborn full-term infants following a difficult labor and all premature infants were given some adult blood immediately following birth, such a transfusion might overcome shock, supply the needed vitamin K and prothrombin, as well as furnish nourishment and fully developed red corpuscles to be utilized in carrying on the circulatory functions. The effectiveness of blood transfusions promptly given to combat shock and hemorrhage in battle injuries has been proved beyond a doubt.

Our experience in transfusing thirty-four newborn infants by way of the umbilical vein, with mother's blood as the adult blood provided, was reported in 1944[1]; subsequent use of cord transfusions with mother's blood is reported here.

Another hazard to the newborn infant is erythroblastosis. It has been supposed that the Rh factor is involved in the development of this disease, and that one in thirty to fifty of the infants of Rh-negative mothers may be expected to develop it. It would seem that the Rh factor alone does not determine or is not alone present in the development of the disease. Even more prognostic of its occurrence, particularly when found in infants of Rh-negative mothers, is a high count of normoblasts in the cord blood immediately or soon after birth.

Since cord transfusions have proved of value in combating shock and hemorrhage in premature infants and in full-term babies after a hard labor, their value would seem likely in actual or prophylactic treatment of erythroblastosis, a blood dyscrasia, the probable development of which can be expected to some extent among Rh-negative mothers, particularly multipara, and to a larger extent among infants whose cord smears show a high count of normoblasts. Cord transfusions in seventy-eight infants of Rh-negative mothers are reported, together with a discussion of 601 cord smears.

The technique of cord transfusion is also described.

From the Obstetrical Department of the Methodist Hospital.
This study aided by a grant from the Lindridge Research Fund.

TECHNIQUE OF CORD TRANSFUSION

The technique of giving mother's blood to newborn infants by way of the umbilical vein is not difficult, and relatively few conditions make such transfusion impossible.

Mother's blood is preferred because at the time of delivery it contains more prothrombin and vitamin K than the average individual's, the vitamin K having been reinforced by administration during labor. If mother's blood is used only once, as is usually the case, it is not necessary to match the blood before giving the cord transfusion. Even if incompatible and though there may be some reaction, this one transfusion will assist the baby, since the blood will remain in the circulation long enough to exert its beneficial effect. The reason for this is the absence of agglutinins in the baby's blood at birth other than those derived from the mother.

The blood should be withdrawn before the birth under sterile precautions and placed on the delivery table. A 50 c.c. syringe is used containing sufficient citrate to insure against clotting in the syringe; 5 c.c. of a 2 per cent solution of sodium citrate is enough for 35 c.c. of blood. If more than 35 c.c. are withdrawn there is danger of the blood's clotting and clogging the needle, thus making the transfusion impossible without straining the blood. If 50 c.c. of blood are to be used, then 7 or 8 c.c. of the citrate are advisible. When the citrate is first drawn into the syringe, the entire length of the barrel should be moistened with it by withdrawing the plunger of the syringe and allowing the solution to come in contact with the entire inside of the barrel. This seems like a needless precaution, but when a large syringe is used, considerable pressure is needed to force the blood into the umbilical vein, and if the blood comes in contact with the barrel and plunger before being citrated, the plunger is very likely to stick and make the transfusion either very difficult or impossible. If the blood has not been withdrawn before delivery and a transfusion is deemed necessary, then, if the syringe is easily available, it is often possible to draw the blood after the baby is born and give the cord transfusion. This has been done frequently with complete success.

The amount of blood given depends upon the size of the baby and the reason for its use. In giving 500 c.c. of blood to a woman weighing 125 pounds, we give 4 c.c. per pound of body weight. The correct amount for a baby is about 10 c.c. per pound of body weight. A good many of our early transfusions were insufficient, and in several cases the baby's life may have been lost as a result. An insufficient amount was especially likely to be given twins, the amount of blood withdrawn being about enough for one baby; instead of giving it all to one twin, the amount was divided, with neither receiving an adequate amount. We recently delivered twins, each weighing over 6 pounds. We had two syringes with 35 c.c. of blood available. Following the cord transfusion, their progress was excellent.

It is preferable to inject the blood before separating the baby from the mother. The baby is placed on the mother's abdomen or is held with the head

down by an assistant. The cord is clamped and the blood injected into the umbilical vein. The cord should be steadied with the left hand, the barrel of the syringe grasped with the right, and the blood injected by making pressure on the plunger with the chest.

Great care should be taken after entering the cord vein. Should the point of the needle perforate the thin-walled vein, the blood will be injected into the substance of the cord, and a diffuse localized area of hemorrhage will appear. If this happens, the transfusion may be attempted again at a point nearer the baby's body, provided the first attempt was made far enough away from the naval. It is important to select the first site at a maximum distance, usually about twelve inches, to allow for subsequent trials. We have recently found a large, short-bevel, Fordyce needle obviates danger of vein injury.

Delay may make transfusion by the cord route impossible. The blood may enter the vein, the vein distending as far as the umbilicus, but will fail to enter the baby's body.

At times it is advisable to separate the baby from the mother before doing the transfusion. On cutting the cord it is likely to collapse and the veins are hard to identify. If the cord is milked toward the clamp, enough blood can be collected to identify the vein.

The giving of blood seems to have no ill effect on the baby. Frequently the respirations are stimulated, and the baby, previously pale, becomes pink.

CORD TRANSFUSIONS

The first cord transfusion at the Methodist Hospital was given in 1940 to a premature infant (Case 4). The first published report on cord transfusions was in 1944,[1] when thirty-four cases were presented, eighteen in premature infants weighing less than 5½ pounds and sixteen infants weighing over 5½ pounds. There were four deaths, all under thirty-seven weeks' gestation. During 1944 there were 189 cord transfusions with 174 living babies. Ninety-nine cord transfusions were done in premature infants; twenty-one in full-term infants following difficult labor or delivery and seventy-eight in infants of Rh-

TABLE I. TOTAL CORD TRANSFUSIONS, 1940 THROUGH MARCH 1945

					DEATHS			
	PREMATURE INFANTS (37 WK. OR UNDER)	FULL-TERM	MOTHERS RH–	TOTAL	PREMATURE INFANTS (37 WK. OR UNDER)	FULL-TERM	MOTHERS RH–	TOTAL
1940 through 1943	18	16	–	34	4	–	–	4
1944	99	21	78*	189	15	–	2*	15
Jan, Feb., and March, 1945	22	4	32	58	1	–	–	1
Total	139	41	110	281	20	–	2	20

*Nine of the babies with mothers Rh– were premature infants and have been included in this group as well. Total count of cord transfusions does not include these duplications.

negative mothers. Nine of the last group were also premature infants and reported in that group; thus the total of cord transfusions is nine less than the sum of the three groups. Through March, 1945, fifty-eight cord transfusions have been done.

CORD TRANSFUSIONS IN PREMATURE INFANTS

In 1944, cord transfusions were given to ninety-nine infants of thirty-seven weeks' gestation or under. Of these, fifty-five weighed 5½ pounds or under and forty-four more than 5½ pounds (Table II).

Of the fifty-five in the first weight group, i.e., those weighing 5½ pounds or less, twelve babies weighing between 5 and 5½ pounds all lived; twenty-six weighing from 4 to 5 pounds, and of these three died; of eleven weighing between 3 and 4 pounds, and of these five died. Mortality was 100 per cent in the group weighing 3 pounds and less; two weighing from 2 to 3 pounds, four weighing from 1 to 2 pounds. The total number of deaths was fourteen and nine of these occurred in infants of less than seven months' gestation; only two weighed over 4 pounds; one was a twin who lived for fifteen days and the other, who weighed 4 pounds, 15 ounces, was of thirty-three weeks' gestation, and was delivered following a severe pyelitis of his mother. He received 35 c.c. of his mother's blood by cord transfusion and died in fourteen hours. The mother was Rh positive.

Of the forty-four in the second group, i.e., those weighing over 5½ pounds, there was one stillbirth. The blood had been drawn from the mother thinking the baby would be born alive; the cord transfusion was given with no difficulty. The mother was a diabetic patient.

Weight is apparently not always a true index of ability to survive. An infant who might have weighed 10 or 11 pounds at 9 months, though born prematurely at 7 months and weighing 6 pounds, is, nevertheless, premature.

CORD TRANSFUSION FOLLOWING DIFFICULT DELIVERY

The greatest danger to the infant following a long labor or difficult delivery is cerebral hemorrhage. If this danger could be met, we might not be so anxious to do cesarean sections when the baby seems a little large or the cervix does not dilate as easily as we imagine it should.

TABLE II. CORD TRANSFUSIONS IN PREMATURE INFANTS IN 1944

	BIRTHS	DEATHS	PER CENT
37 weeks and under	99	14	14.1
Over 5½ pounds			
Live births	43	–	0.0
Stillbirths	1	–	–
5½ pounds or under			
Live births	55	14	25.4
5½ pounds or under	55	14	25.5
5 to 5½ pounds	12	0	0.0
4 to 5 pounds	26	3	11.5
3 to 4 pounds	11	5	45.4
2 to 3 pounds	2	2	100.0
1 to 2 pounds	4	4	100.0

During 1944, twenty-one cord transfusions were given following difficult deliveries. Twelve were posterior positions, eleven were delivered by medium forceps and thirteen were rotated either by forceps or manually. Eleven of the babies weighed over 8 pounds. In many of these cases the baby's condition was poor, but there were no deaths.

In the 1943 report, sixteen full-term infants were given cord transfusions on similar indications, with no deaths.

CORD TRANSFUSIONS IN BABIES OF RH-NEGATIVE MOTHERS

After the successful use for a number of years of cord transfusions in premature babies and in full-term infants threatened with hemorrhage after a difficult labor, it was thought the method might save some of the babies born of Rh-negative mothers who were affected by the Rh factor. There has been much discussion in both general and scientific magazines about probable death from erythroblastosis of infants of Rh-negative mothers.

Under a grant from the Lindridge Fund, grouping and typing of the blood of maternity patients was begun; at present such tests are done on all ward patients and many private patients. The technique is simple. At the hospital, when taking blood for the blood count of ward patients, the technician expresses several more drops, collecting them in a tube containing 5 c.c. of normal saline. In the doctor's office, when the blood is drawn for the Wassermann, before removing the needle from the syringe, a few drops are forced into the saline bottle; then the needle is removed and the remainder of the blood used for the Wassermann. At the present time, we are drawing enough blood when the Wassermann is taken so that 3 or 5 c.c. of whole blood is sent to the laboratory for grouping and the Rh factor. With both ward and private patients, after the blood is grouped and typed, the report is given the physician on the detachable part of a label he originally filled out. A card stating blood group and Rh factor is also given the patient, somewhat like the "dog tag" given servicemen (Figs. 1 and 2).

During 1944, 1,910 blood specimens were examined; 296, or 15.2 per cent, were Rh negative, and 137 of these patients were delivered in 1944. Two, or 3 per cent, of the babies of these women could be expected to develop some form of erythroblastosis; if the mother was a multipara, probability was more certain. Practically nothing has been suggested to be given the mother as a prophylactic against the disease in her child. The usual treatment of the child, once the disease is manifest, is transfusion with blood of an Rh-negative donor. The disease is sometimes unrecognizable at birth, and one is not looking for it unless the mother is known to be Rh-negative. If the vernix is yellow or the liquor amnii is stained yellow, erythroblastosis should be suspected and a cord smear or blood count made immediately. Even these may be normal and the baby still develop erythroblastosis.

Of the babies of the 137 Rh-negative mothers, seventy-eight were given cord transfusions using mother's blood, and fifty-nine were not. According to Levine[2] cases for transfusion should be selected on the basis of increasing degree of immunization, i.e., agglutinins with blocking antibodies. There were eight cases

of erythroblastosis or some blood dyscrasia diagnosed as erythroblastosis, three in the transfused group, five in the group not transfused. The three infants in the transfused group recovered; there were, in addition, two deaths, both among premature infants, in which diagnosis of erythroblastosis was not made. In the group not transfused, two of the five died, three recovered.

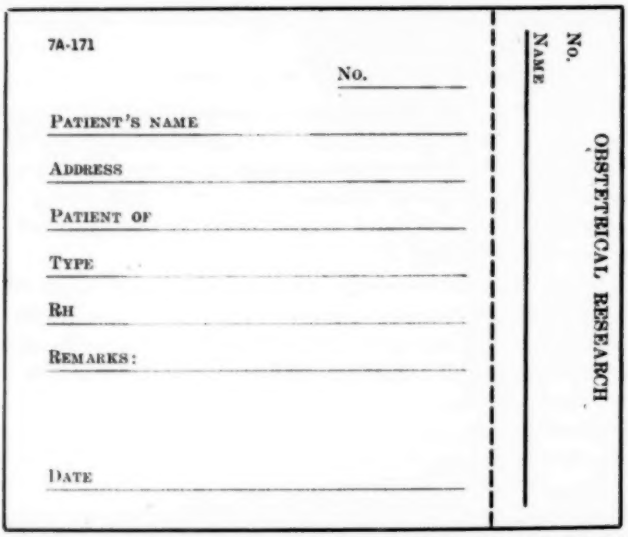


Fig. 1.—This is a reproduction of a gummed label with detachable strip which is distributed to the doctors, filled out by them, attached to the blood specimen, and sent to the laboratory. Blood type and Rh factor are filled in and the label along with the patient's card, is returned to the doctor.

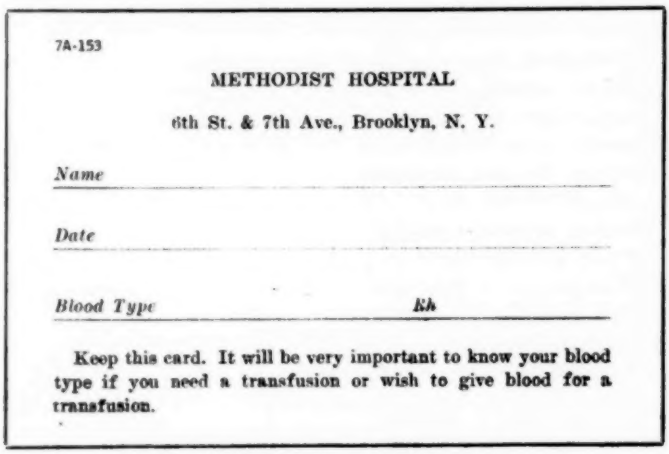

7A-153
METHODIST HOSPITAL
6th St. & 7th Ave., Brooklyn, N. Y.
Name
Date
Blood Type
Rh
Keep this card. It will be very important to know your blood type if you need a transfusion or wish to give blood for a transfusion.

Fig. 2.—Reproduction of patient's card.

The two deaths in the transfused group have been included in the report on premature infants. One was the infant weighing 4 pounds, 15 ounces, gestation thirty-four weeks, delivered by cesarean section. Fifty cubic centimeters mother's blood were given by cord transfusion, the baby dying within fourteen hours. The Rh-negative mother had lost one baby at seven and one-half months and had also had a six months' stillbirth. The second premature baby who died weighed 3 pounds, 9 ounces, and was of thirty-one weeks' gestation; he was in critical condition at birth and lived only one hour, ten minutes. The Rh-negative mother was a gravida i, blood group 0. The baby was Rh positive, blood group B. Cord smear showed 46 normoblasts. At autopsy internal hydrocephalus was found.

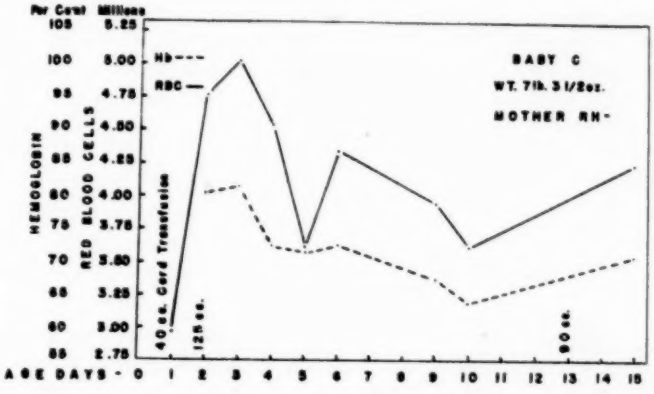


Fig. 3.—Erythroblastosis fetalis, Baby C.

One of the babies in this transfused group who developed erythroblastosis and recovered was a full-term male child weighing 7 pounds, 3½ ounces. He had received 40 c.c. mother's blood by cord transfusion. The mother, who had had one normal child and lost a premature infant of six months' gestation, who had lived three days, was Rh negative; the father and baby, Rh positive. Condition was fair at birth, but the skin soon became yellow and the spleen was palpable one fingerbreadth below the costal margin. The first blood count had showed 2,900,000 red cells with marked change in size and shape of the cells but no normoblasts. On the day after delivery, the baby was given 125 c.c. of blood from a professional Rh-negative donor. The count increased to 4,760,000 with 25 nucleated red cells per 100 white cells. Two days later the red cells were 5,050,000 with 6 nucleated red cells. At 9 days of age the count had dropped to 3,600,000, and at 42 days to 2,830,000. The baby made an excellent recovery. (Baby C, Fig. 3.)

Two others of the transfused group were thought to have some blood dyscrasia, diagnosed as erythroblastosis. Normoblast count was above 15. Both recovered.

In the group not given cord transfusions, there were five cases of erythroblastosis with two deaths. The first of the two infants who died was full term, condition good at birth. The mother was Rh negative; the father and baby, Rh positive. The mother had had a normal baby in 1941; she had had a hemorrhage following delivery and was transfused. At the age of 28, June 20, 1944, she was delivered of her second child. The baby nursed well until the third day, when he became very jaundiced; the liver was palpable one fingerbreadth below the costal margin. The blood count was 4,860,000, with no normoblasts. The baby was given 25 c.c. of blood from an Rh-negative donor but died the following day. Autopsy showed hematopoiesis in the liver.

The second baby in the nontransfused group who died was delivered by cesarean section Dec. 12, 1944. The mother had had one normal child by cesarean section, was 28 years old, and Rh negative. The baby weighed 6 pounds, 15 ounces, and seemed in good condition at birth. Red cell count, however, was 4,970,000, with 142 normoblasts. Nine hours after birth, the baby was given 105 c.c. of blood from an Rh-negative donor of the same blood type. The following day the red cell count was 5,230,000 and the normoblasts 158 per 100 white cells. The skin became yellow and the spleen palpable. The condition soon became critical. Coffee-ground vomitus and blood were coming from the nose and mouth, and the baby died on the second day.

Three other infants with a count of more than 15 normoblasts, in whom a diagnosis of erythroblastosis was made, received early intravenous transfusions and lived.

The history of the seventy-eight Rh-negative mothers whose babies were given cord transfusions of mother's blood showed that forty-one were multiparas; thirty-four of these multiparas had previously had full-term pregnancies, four premature babies, ten miscarriages, three stillbirths, and with four the babies had died. Thirty-seven were primiparas. (Table III.)

TABLE III. PARITY IN 137 MOTHERS RH–

	CORD TRANSFUSION		
	YES	NO	TOTAL
Gravida 1	37	25	62
Gravida 2	23	21	44
Gravida 3	12	8	20
Gravida 4	3	3	6
Gravida 5	3	2	5
Total	78	59	137

Thirty of the seventy-eight patients were apparently over term when delivered; ten, forty-two weeks, and twenty, forty-one weeks. Twenty-three were delivered at term, forty weeks. There were nine under thirty-seven weeks, including the two whose babies died, already reported. (Table IV, A.)

Six of the fathers in this group were Rh negative; in the group not transfused eleven were Rh negative. A comprehensive test of father's blood was not made, however, many of the fathers being in service, or for some other reason their blood not being available for testing. In the transfused group, nineteen

TABLE IV, A AND B. SEVENTY-EIGHT CORD TRANSFUSIONS; MOTHERS RH–

A. GESTATION		B. AMOUNT OF BLOOD TRANSFUSED	
42 weeks	10	?	7
41 weeks	20	10 c.c.	2
40 weeks	23	15 c.c.	1
39 weeks	10	20 to 25 c.c.	5
38 weeks	5	30 c.c.	7
37 weeks	1	35 c.c.	9
Under 37 weeks	9	40 to 45 c.c.	30
		50 c.c.	17
Total	78	Total	78

TABLE V. RH FACTOR IN 137 BIRTHS

	CORD TRANSFUSIONS		
	YES	NO	TOTAL
Mother Rh–	78	59	137
Father Rh–	6	11	17
Father Rh+	41	11	52
Father not tested	31	37	68
Baby Rh–	19	5	24
Baby Rh+	42	12	54
Baby not tested	17	42	59

babies of sixty-one tested were Rh negative, and forty-two, Rh positive; five in the nontransfused group were Rh negative, and twelve, Rh positive among seventeen tested (Table V).

The amount of mother's blood given in the cord transfusion varied from 10 c.c. to 50 c.c. Thirty received from 40 to 45 c.c., and seventeen, 50 c.c. (Table IV, B). In the case of the very small amounts, the transfusion was unsuccessful and an adequate amount of blood could not be given. However, if any blood at all was given by the cord route, the case was counted as a cord transfusion.

Administration of blood via cord transfusion at birth from an Rh-negative mother to her baby as an aid in the treatment of erythroblastosis is contrary to the generally accepted rule of using Rh-negative donor's blood. The infant who received a cord transfusion, in whom erythroblastosis developed (Baby C), had no normoblasts in the blood following the cord transfusion, though jaundice was marked. Twenty-five normoblasts were found the second day. It may be argued that the jaundice in this case was caused by reaction to the mother's blood. If this is so, why did not a similar reaction occur in the other cases similarly transfused?

Three interesting cases seen in 1945 and one in 1944 are discussed immediately following. In the first, the baby was tranfused the second day with 90 c.c. of mother's blood; later it was discovered the mother was Rh negative, her blood having an exceptionally high agglutinin titer. There was no reaction. The second is a case of jaundice in a cord-transfused infant of an Rh-negative mother, with recovery; the third, a case of jaundice in an infant of an Rh-negative mother, not cord-transfused, with recovery. The fourth reports death of three of five infants, both parents Rh positive.

CASE HISTORIES

CASE 1.—Observed this year. The mother had had a normal baby by her first husband seven years before. When she was delivered in 1945, it was thought she was Rh positive. The baby was not given a cord transfusion. He very soon became extremely jaundiced and was thought to have an obstruction of the bile ducts. He was given 90 c.c. of his mother's blood on the second day and showed much improvement. The blood count was normal until the eighth day, when it was found to have dropped to 4,200,000 with a hemoglobin of 80 per cent. When the baby was 14 days old, the red cells were 2,700,000 and the hemoglobin 60 per cent. He was given 90 c.c. of blood from a professional Rh-negative donor. The blood of the mother was tested by Dr. Levine, who found the agglutinins of a titer of 1:80. It is rather hard to explain how this baby had been able to take so much of his mother's blood, 90 c.c. on the second day, without getting some reaction (Baby A, Fig. 4).

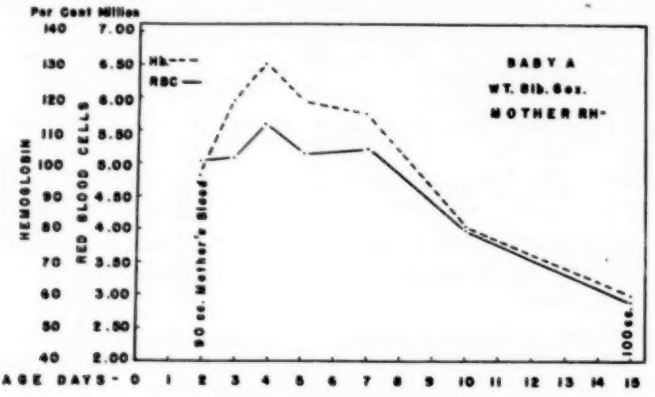


Fig. 4.—Erythroblastosis fetalis. Baby A (Case 1).

CASE 2.—The baby was born in January, 1945. Mrs. S. was a para i, gravida ii, 25 years old, white, Rh negative. The baby was a full-term female child, weighing 9 pounds, 2 ounces, and was given 40 c.c. of mother's blood by cord transfusion. Examination of the blood on the day of delivery showed 3,000,000 red cells; hemoglobin, 82 per cent. The baby was markedly jaundiced. The following day, 125 c.c. of blood from a professional Rh-negative donor of compatible blood group were given. After the transfusion, the red cells were 6,400,000; hemoglobin, 113 per cent. The baby made an uneventful recovery. According to Dr. Levine, this mother had weak anti-Rh agglutinins and weak blocking antibodies.

CASE 3.—Baby L, born Dec. 4, 1944. The mother was Rh negative. She had had a normal baby in 1937, a miscarriage at two and one-half months in 1939, and a baby who died on the third day in 1940. This baby, a boy, weighed 7½ pounds, and condition at birth was good. Examination of the blood showed 3,820,000 red cells; hemoglobin, 60 per cent; 375 normoblasts. The baby was born at 9 A.M.; at 11:30 A.M. 40 c.c. of his mother's blood were given. At 11 P.M. red cells were 3,210,000; hemoglobin, 50 per cent; and 510 normoblasts. Fifty-five cubic centimeters of blood were given. The baby died on the third day. Autopsy showed both liver and spleen enlarged; throughout the liver were clumps of nucleated red cells.

Dec. 4, 1944, the mother was delivered of a supposedly full-term child weighing 5 pounds, 15 ounces. The baby was slightly jaundiced; the spleen, enlarged; and the blood showed 318 normoblasts. It was impossible to give the baby a cord transfusion. Seventy cubic centimeters of blood from an Rh– negative donor were given, and the following day red

cells were 4,800,000; hemoglobin, 90 per cent; nucleated red cells, 63. On December 8, the fifth day, red cells were 3,910,000; hemoglobin, 69 per cent; nucleated red cells, 21. Seventy-five cubic centimeters of blood from an Rh negative donor were given, and the baby made an uneventful recovery.

The baby had a reaction from the second transfusion which looked very serious for a while, but we found that he had had a bottle just before the transfusion, had vomited and aspirated some of his dinner. He was soon all right. We would have given more blood if this had not occurred (Baby L, Fig. 5).

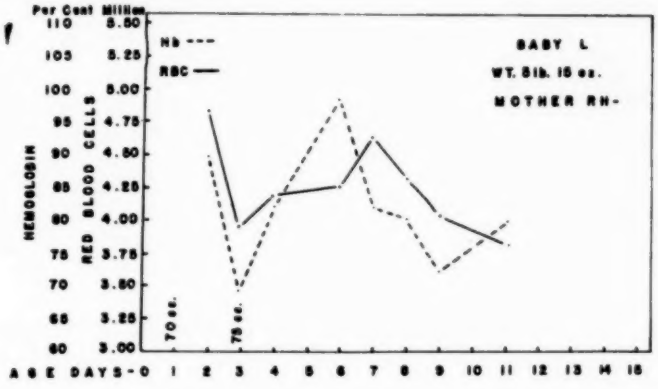


Fig. 5.—Erythroblastosis fetalis, Baby L (Case 3).

CASE 4.—The following case is one in which both parents were Rh positive; it is difficult to explain the loss of three of five babies.

Mrs. D. A. had lost two babies—one at eight months who had lived for twelve hours, one at seven months who lived for five hours. On Sept. 1, 1940, she was delivered at Methodist Hospital of a seven months' baby weighing 4 pounds, 4 ounces; he was transfused through the umbilical cord with 40 c.c. of his father's blood. This baby lived and is now 5 years old and a normal child. This was the first baby to receive a cord transfusion, and the case was reported in 1944, together with the mother's fourth delivery, in June 1943, when she was delivered of a baby weighing 6 pounds, 4 ounces, of thirty-six weeks' gestation. The baby was given a cord transfusion, using his father's blood, but when 20 c.c. were injected, the baby showed signs of a reaction and the transfusion was discontinued. The baby died in twenty-five minutes. Autopsy showed cause of death was hemorrhagic disease.

On March 18, 1945, this patient, now 34 years old and a gravida v, was delivered of a baby weighing 6 pounds, 11 ounces. The baby was given a cord transfusion of 40 c.c. of his mother's blood without any reaction and is apparently a normal baby. During this pregnancy the mother received ¼ grain protiodide of mercury twice daily, 20 minims of wheat germ oil daily, and during the last month one milligram of vitamin K daily. She was delivered at thirty-eight weeks, her only pregnancy to go into the ninth month.

NORMOBLASTS FOUND IN CORD SMEARS

The value of cord blood smears taken at birth has not been stressed nor is the significance of an increase in number of normoblasts sufficiently appreciated. The number of normoblasts is supposedly increased in certain conditions, such as diabetes, hemorrhage, and asphyxia; if the mother is Rh negative, we should suspect some blood dyscrasia, possibly erythroblastosis.

In 1944, a study of 538 routine cord smears showed that 279, or 51.9 per cent, contained no nucleated red cells, seventy contained only 1 in 100 white cells; 236, or 43.9 per cent, 1 to 15. There were twenty-three instances, 4.3 per cent, in which more than fifteen normoblasts were found (Table VI).

A study of sixty-three smears from the cord blood of babies of Rh-negative mothers showed considerable difference. Only nine smears, 14.3 per cent, contained no nucleated red cells, only four 1, and forty-three, or 68.3 per cent, from 1 to 15. There were eleven, or 17.5 per cent, that contained more than 15 (Table VI).

TABLE VI. NORMOBLASTS FOUND IN 601 CORD SMEARS

NORMOBLASTS	ROUTINE SMEARS	PER CENT	MOTHERS RH–	PER CENT
None	279	51.9	9	14.3
1	70		4	
2	51		7	
3	26		5	
4	20	43.9	3	68.3
5	15		5	
5 to 10	37		14	
10 to 15	17		5	
15 to 30	12		7	
30 to 40	4		2	
40 to 100	6	4.3	1	17.5
Over 100	1		1	
Total	538		63	

These thirty-four smears with more than 15 normoblasts deserve study (Table VII). In twenty-three the mothers were Rh positive; in eleven, Rh negative; nine of the infants of the Rh-negative mothers received cord transfusions. There were five deaths and one stillbirth among the thirty-four infants; five of the six mothers were Rh positive; one, Rh negative.

TABLE VII. THIRTY-FOUR CORD SMEARS SHOWING MORE THAN FIFTEEN NORMOBLASTS

Rh Factor		Mortality	
Rh–	11	Stillbirth	1
Rh+	23	Died	5
Parity		Lived	28
Primapara	9	Transfusions	
Multipara	25	Cord	9
Gestation		Later	6
Premature	7	None	20
Full-term	27	Duplications	1

The mother of the stillborn child was Rh positive; the baby was full term, weighed 8 pounds, 2 ounces, and had 37 normoblasts. Four mothers of the five infants who died were Rh positive and none of the infants received cord transfusions. One weighed 1 pound, 13 ounces, and had 32 normoblasts. The second weighed 10 pounds, 12 ounces, and had 44 normoblasts; this baby lived only a short time following a difficult breech delivery. The third was full term, weighed 7 pounds, 7 ounces, and lived only one hour. Increase in the normoblasts in these last two cases may have been due to asphyxia. The mother of the fourth baby, also Rh-positive, had had three children, all small, the last

one weighing 5 pounds, 5 ounces. The baby seemed in good condition at birth; when he was 12 hours old he had bloody vomitus. He was transfused with 45 c.c. of his mother's blood but died soon after. Only the mother of the fifth baby was Rh negative, and this baby had had a cord transfusion. He was a premature infant, of thirty-one weeks' gestation, weight was 3 pounds, 9 ounces, and the child was in critical condition at birth and lived only one hour, ten minutes. Cord smear showed 46 normoblasts. The mother was a gravida i, blood group 0. The baby was Rh positive, blood group B. At autopsy internal hydrocephalus was found.

Six of the total of eight cases of erythroblastosis or blood dyscrasia diagnosed as erythroblastosis in the 137 infants of Rh-negative mothers occurred in babies with high normoblast count. The two in which there was no increase are (1) the premature infant of thirty-four weeks, delivered by cesarean section and dying within fourteen hours; this infant had received a cord transfusion; (2) the full-term infant in the nontransfused group, markedly jaundiced but with no normoblasts, who died on the fourth day.

SUMMARY

1. A total of 189 cord transfusions were done during 1944 with 174 living babies.

2. Ninety-nine premature babies received cord transfusions of mother's blood, with fourteen deaths. Six of these weighed less than 3 pounds; nine were twenty-eight weeks' gestation.

3. Twenty-one babies were transfused following long labors or difficult deliveries, with no deaths.

4. The blood was grouped and the Rh factor determined in 1,910 women. Of these, 294 were found to be Rh-negative and 137 were delivered in 1944 with the loss of four infants, two in the group of seventy-eight receiving cord transfusions, two in the group of fifty-nine not receiving such transfusions.

5. The babies of seventy-eight Rh-negative mothers received cord transfusions of mother's blood. There were two deaths, both premature infants. Three cases of erythroblastosis were diagnosed in the group, with recovery.

6. Of fifty-nine babies of Rh-negative mothers not given cord transfusions, there were five cases of erythroblastosis, with two deaths. One of the babies was very jaundiced, with no normoblasts; the other had 158 normoblasts to 100 white cells.

7. A study was made of 601 cord smears; 288 contained no normoblasts, thirty-four more than 15. Among these thirty-four infants there were five deaths and one stillbirth. Five of the six mothers were Rh positive; one Rh negative. Of the eleven infants of Rh-negative mothers in the group of thirty-four, nine received a cord transfusion, with one death, a premature infant.

8. A case is reported in which 90 c.c. of blood from an Rh-negative mother of high titer, 1:80, was given to her baby for marked jaundice with definite improvement in the baby's condition.

CONCLUSIONS

During the last five years, we have given 281 cord transfusions to newborn babies with the loss of only twelve viable infants. Our technique has been considerably improved since the beginning, and it is seldom that the transfusion is not successful. We believe that the giving of mother's blood is a means of saving many premature babies and those at term born after a long labor or difficult delivery. The transfused blood tends to overcome anoxia, stimulate the respirations, and give to the premature baby adult red corpuscles which are able to carry oxygen to the tissues.

We are now giving cord transfusions to babies born of Rh-negative mothers when the mothers have had a previous pregnancy. Use of mother's blood rather than donor's is contrary to the general rule, but so far the mother's blood seems to agree with the babies. Cord transfusions may be useful in anticipation of the development of erythroblastosis in infants of Rh-negative mothers or in its treatment when present at birth.

I wish to express my gratitude to Dr. Philip Levine for personal interest and helpful suggestions in editing this paper. Dr. Levine has checked a large number of the blood specimens from Rh-negative mothers.

The great majority of the cord transfusions were given by our resident staff. Dr. Isabelle Seismann, Dr. Norma Jones, and Dr. Frank R. Hurlbutt, Jr., and to them I am deeply indebted.

REFERENCES

1. Mayes, H. W.: Am. J. Obst. & Gynec. 48: 36, 1944.
2. Levine, Philip: Personal communication.

494 First Street

ADDENDUM

There have been 117 additional cord transfusions between April 1, and Dec. 1, 1945. Fifty-three of the transfusions were given to babies of Rh– mothers, using mothers' blood, making a total of 85 such transfusions this year with the loss of no viable babies from these mothers.

The total number of cord transfusions of mothers' blood given to their babies is 398. Two hundred three of the babies were premature and 163 were babies of Rh– mothers.

ANTI RH AGGLUTININS IN THE MATERNAL BLOOD WITHOUT SYMPTOMS OF HEMOLYTIC ANEMIA IN THE NEWBORN INFANT

ALTON GOLDBLOOM, M.D., AND HERBERT LUBINSKI, M.D.
MONTREAL, QUEBEC

THE presence of anti Rh agglutinins in the serum of a pregnant or parturient woman nearly always is followed by a more or less severe hemolytic anemia in the newborn infant. Doekeray and Sachs[1] however have reported four cases in which the mother's sera contained considerable amounts of what were assumed to be anti Rh agglutinins and yet the newborn infants did not exhibit clinically demonstrable manifestations of hemolytic disease. In two of their cases it is not clear whether true anti Rh agglutinins or some other atypical agglutinins were present. In the third case anti Rh agglutinins were present but the records do not state whether the infant's blood was examined for the presence of anemia or hemolysis. In the fourth instance anti Rh agglutinins were found four years after the last delivery and following a transfusion reaction. Four children born prior to this accident gave no history of having suffered from hemolytic anemia. However, a slight degree of jaundice may have been regarded as physiologic or may have been completely overlooked.

We had the opportunity of observing and studying a case in which anti Rh agglutinins were present in the mother's serum although the infant did not demonstrate any of the symptoms of hemolytic anemia of the newborn.

A. C.,* a white woman aged 25 years, was delivered of her third child, a boy weighing 7 pounds, 11 ounces. The delivery was at term and uneventful. Routine testing of the mother's and of the infant's blood revealed:

Mother: group O Rh negative
Infant: group O Rh positive

Tests of the undiluted serum of the mother with several specimens of known Rh positive red cells (including the cells of her own infant) gave a positive reaction ranging in intensity from ± to ++, whereas Rh-negative cells did not show any agglutination. The husband and the two older sons (5 and 3 years old, respectively) also belonged to group O and were Rh positive. These two children are reported in the records of the hospital as having been jaundiced from the third and fourth day of life, respectively, until the seventh day. Both children have developed normally and are in good health.

The newborn baby was kept under close observation. No sign of jaundice could be found during the newborn period and none was reported to us later by the family physician. Red cell counts and hemoglobin estimations during the period of hospitalization are listed in Table I.

The van den Bergh reaction done with cord blood showed: direct, 1.13 and indirect, 3.98. The weight of the infant was on the increase when the baby left the hospital. According to current reports the child is progressing normally.

From the Department of Pediatrics and the Pathological Laboratories of the Jewish General Hospital.

*The case history is presented through the courtesy of Dr. J. Goldberg.

TABLE I

	DAY OF LIFE							
	1	2	3	4	5	7	8	9
Number of red cells (Millions/cu.m.)	6.8	6.0	5.2	4.8	5.0	4.8	4.5	4.5
Hemoglobin (Gm./100 c.c.)	20.3	19.3	18.7	18.4	17.5	17.2	18.4	18.1

In a consecutive series of 1,402 deliveries at the Jewish General Hospital in which Rh typing of mother and newborn baby has been performed, the combination of Rh-negative mother and Rh-positive infant was encountered ninety-three times. In each of these cases the serum of the mother was tested for the presence of anti Rh agglutinins, using the infant's red cells (when possible) and several other specimens of compatible Rh-positive cells. Only in the case here reported were anti Rh agglutinins found without any sign of hemolytic anemia in the newborn infant, whereas in eight other cases the finding of agglutinins in the mother's serum was accompanied by a more or less severe hemolytic disease in the baby.

Since anti Rh agglutinins have usually not been demonstrated in the infant's blood by tests in vitro, it is difficult or even impossible to determine whether any anti Rh agglutinins have passed through the placenta at least in amounts sufficient to do detectable harm. According to Polayes, Lederer, and Wiener[2] in only 66 per cent of compatible cases do normal isoagglutinins pass through the placenta. Lubinski[3] found a somewhat higher percentage (77.5 per cent of 440 cases). It is therefore possible that the same holds true with regard to the passage of anti Rh agglutins.

There is a discrepancy between the number of combinations of Rh-negative mother and Rh-positive infant and the frequency of hemolytic anemia of the newborn. Thirteen per cent of all matings involve an Rh-negative mother and an Rh-positive father; yet only 0.25 to 0.5 per cent of all deliveries result in infants showing hemolytic anemia. This requires the consideration of certain variable factors in the pathogenesis of the disease in addition to differences in Rh type.

From a serologic point of view these factors may be listed as follows:

1. The antigenic power of an individual Rh factor may vary, as is true of any antigen. The Rh factor seems to be a relatively poor antigen, an assumption which is suggested by the fact that many transfusions stretched over a period of several weeks or several pregnancies are usually necessary to build up enough antibodies for the development of a severe reaction. A further confirmation of this opinion lies in the fact that it is rather difficult to obtain anti Rh sera from animals through artificial immunization.

2. The ability of an individual to produce antibodies is well known to vary greatly as in natural immunization through disease, or by artificial immunization through vaccination. This applies as well to immunization by the Rh factor.

3. The amount of antigen that enters the maternal circulation may vary in different cases and may be nil in some. Some authors assume that damage to the placental barrier is necessary for the transmission of the antigen. This

opinion is open to question, chiefly because if this were true, such damage must be assumed in each successive pregnancy in which hemolytic anemia occurs. Moreover, if this were true, a mother with a blood group incompatible with that of her fetus should show a great increase in the titer of normal isoagglutinins; but this is not a common observation.

4. The amount of antibody which passes through the placenta from the mother's circulation into the blood stream of the fetus varies widely in different cases. This is illustrated by the fact that the titer of normal iso- and hetero-agglutinins found in cord blood varies greatly. According to Wiener and Silverman[4] the proportion of titers in maternal blood compared to the titers in cord blood is generally between 8:1 and 12:1. However, one of us (L) has found (in a series of experiments to be published elsewhere) that wider variations from the average than those given by Wiener and Silverman can be found not infrequently. Two of the most striking examples are given in Table II.

TABLE II

TITER OF ISOAGGLUTININS		TITER OF ISOAGGLUTININS		RATIO
Case 1136	1/16 000	Case 1136	1/16	1000
Mother	1/512	Baby	1/1	512
Case 1453	1/8	Case 1453	1/2	4
Mother	1/256	Baby	1/1	256

Furthermore, it seems that a continuous flow of small amounts of antigen over a long period is of greater importance in the causation of the hemolytic disease than the influx of large quantities over a short period.

5. Unknown factors in the fetus, which may be called disposition, seem to be of importance as well. This is clearly shown by Demy's case,[5] in which identical twins of about the same weight reacted quite differently: one infant was severely ill, while the other did not even require a transfusion and showed hardly any clinical signs of disease. It seems unreasonable to assume a difference in the transmitted quantity of antibodies as the cause of differences in the clinical picture. In a small number of tests, identical twins have shown identical titers of normal antibodies.[3]

SUMMARY

A case is presented in which the Rh-positive infant of an Rh-negative mother demonstrated no clinical or laboratory evidences of a hemolytic anemia of the newborn, although anti Rh agglutinins were shown to be present in the maternal blood at the time of delivery.

REFERENCES

1. Dockeray, G. C., and Sachs, H.: J. Immunol. 48: 241, 1944.
2. Polayes, S. H., Lederer, M., and Wiener, A. S.: J. Immunol. 17: 545, 1929.
3. Lubinski, H. H.: Unpublished data.
4. Wiener, A. S., and Silverman, I. J.: J. Exper. Med. 71: 21, 1940.
5. Demy, N. G.: Am. J. Obst. & Gynec. 47: 554, 1944.

EPIDEMIC MENINGITIS AND MENINGOCOCCEMIA TREATED WITH PENICILLIN

RALPH C. LOHREY, M.D., AND JOHN A. TOOMEY, M.D.
CLEVELAND, OHIO

DURING the past year twenty-one patients with meningococcus infections were treated with penicillin intrathecally and intramuscularly or intramuscularly alone in the Division of Contagious Diseases at City Hospital, Cleveland.

The clinical course, the temperature, the decrease of the number of cells in the spinal fluid toward normal levels and the findings in spinal fluid cultures became the criteria whereby it was decided to continue with penicillin or to change the therapy.

In our first series, there were fourteen patients ill with epidemic meningitis. Eleven had positive spinal fluid smears on admission; eleven, positive spinal fluid cultures; three, positive blood cultures; and eight had petechiae. One patient had petechiae only; the other thirteen had either a positive smear or culture, or both.

The first eleven of these patients were given from 10,000 to 15,000 units of penicillin intramuscularly every three hours. Rosenberg and Arling[1] reported that 15,000 units of penicillin given intrathecally caused irritation and meningeal signs. Therefore, only 10,000 units were administered intrathecally in the first eleven cases of this study, the greatest number of intrathecal injections being five and the least three. Three subsequent patients were given daily intrathecal injections of 20,000 units each. The last 3 were given 20,000 units every three hours and 20,000 units intrathecally daily. Two of these had four injections and one only two when the treatment had to be changed. Eight of these fourteen cases responded satisfactorily to intrathecal and intramuscular administration of penicillin, while six did not respond so well. A brief summary of each of the latter cases follows.

PATIENT 1.—J. R. (Case 263264), a white female, aged 22 years, had 38,750 cells in the spinal fluid on admission and a positive spinal fluid smear and culture for meningococci. She was comatose and had numerous petechiae. She was given 10,000 units of penicillin intrathecally for four successive days and 10,000 units intramuscularly every three hours during that time. She was still critically ill at the end of the second hospital day when she was given 100,000 units of meningococcic antitoxin. She showed no response clinically on the fourth day even though the spinal fluid contained only 321 polymorphonuclear cells. Treatment was changed to sulfadiazine on the fifth day; on the sixth hospital day consciousness returned and the temperature began to drop by lysis. This patient had partial deafness.

PATIENT 2.—E. M. (Case 263299), a 14-year-old Negro male, was admitted conscious but with a severe headache. The admission spinal fluid contained only 12 mononuclear cells, from which meningococci were cultured. Blood culture was also positive. He was given 15,000 units of penicillin daily for three days and 10,000 units intramuscularly every three hours. The temperature spiked for five days, dropping slowly to 37.8° C. on the sixth hospital day. Later that day, the temperature suddenly rose to 39° C. and he seemed worse clinically. Penicillin

From the Department of Contagious Diseases City Hospital and the Department of Pediatrics Western Reserve University.

was discontinued and sulfadiazine started. His temperature was normal on the next day and remained at normal levels.

PATIENT 3.—M. H. (Case 263664), a 38-year-old white female, was admitted in a comatose condition with 13,750 cells in the spinal fluid, from which organisms were cultured. She was given a daily intrathecal injection of 10,000 units of penicillin for 5 days and 15,000 units intramuscularly every 3 hours. She had positive cultures up to and including the fifth day when 1,100 cells were found in the spinal fluid. The patient was conscious on the second hospital day, but she had a constant headache and the temperature averaged 38.5° C. for six days following admission. On the sixth hospital day, the treatment was changed to sulfadiazine. The headache disappeared the next day and the temperature dropped to normal, where it remained.

PATIENT 4.—P. F. (Case 264343), a 50-year-old white male, was conscious on admission and had a temperature of 37.4° C. He had 11,150 cells in the spinal fluid and the smears and the cultures were positive. He was given 10,000 units of penicillin every day for three days and 15,000 units intramuscularly every three hours for four days. The temperature rose steadily to 39.4° C. and on the fourth hospital day the patient's condition became worse and he was wildly delirious. There were 5,000 cells in the spinal fluid on the third hospital day. Sulfadiazine was started on the fourth hospital day and the penicillin discontinued. The temperature became normal by the following evening and remained thus thereafter.

PATIENT 5.—P. K. (Case 220431), a 5-year-old white female, was admitted with a history of having had an acute illness resembling meningococcemia. The spinal fluid smear and culture were negative on admission. The blood culture was positive. The temperature was 40.5° C. She was given penicillin, 20,000 units intramuscularly every three hours and 20,000 units intrathecally for two days. On the second hospital day, she became comatose and wildly delirious. The spinal fluid at this time contained 6,400 cells and the smear and culture were positive. There were more petechiae than on admission. On the third hospital day, the spinal fluid showed 8,000 cells and smears were positive. The temperature was 38° C. and the patient was deeply comatose. Treatment was changed to sulfadiazine and meningococcic antitoxin, 50,000 units of which were given on the afternoon of the third day. She began to respond and was only delirious for a time on the fourth hospital day. She was alert on the fifth hospital day and had a normal temperature thereafter.

PATIENT 6.—W. L. (Case 267946), a 46-year-old white male, was admitted delirious and in a comatose condition with a temperature of only 37.9° C. The spinal fluid contained 45,000 cells and the smear and the culture were positive. He was given 20,000 units of penicillin intrathecally for four days and 20,000 units intramuscularly every three hours for the same period of time. He appeared to be the same clinically on the second hospital day and there were 20,000 cells in the spinal fluid. On the third hospital day his temperature rose slightly and, clinically, he was worse, although the number of cells in the spinal fluid dropped to 8,000. It was decided to continue the same treatment. On the fourth hospital day, the temperature rose to 39.8° C. He became deeply comatose and appeared to be moribund. The spinal fluid contained only 2,740 cells, but because of his desperate condition the treatment was changed to sulfadiazine and 100,000 units of meningococcic antitoxin. On the fifth hospital day, he began to respond clinically. On the sixth and seventh hospital days, he was alert again, the temperature still being near 39° C. On the eighth hospital day, he began to have some slight deafness. By the tenth hospital day he was completely deaf. The temperature began to fall, averaging about 38° C. until the fourteenth day, and it was at normal levels by the eighteenth hospital day. On that day and for the next two days, he had periods of hallucinations which cleared by the twentieth hospital day.

It was felt that possibly an inadequate amount of penicillin had been given to these eleven patients, so that the dosage both intramuscularly and intrathecally was raised to 20,000 units in the next three patients. In spite of this, difficulties in treating these patients were encountered as with the preceding

patients. Further, a clear-cut case of meningococcemia progressed on to purulent meningitis, a meningitis not prevented by penicillin in the dosages used.

In this small series, some patients did not respond to penicillin therapy. Our observations are that patients treated with penicillin respond more slowly than do those treated with sulfadiazine and antitoxin, the standard treatment in our hospital.[2]

In a series of four patients, the meningitis was treated with penicillin intramuscularly only. A brief summary of each of these cases follows.

PATIENT 15.—C. S. (Case 266674), a 2½-year-old white male, was admitted acutely and seriously ill, but conscious. There were only 60 cells in the spinal fluid, all of which were polymorphonuclears. He had petechiae and the blood and spinal fluid cultures were positive. He was given penicillin, 15,000 units every three hours for a total of 390,000 units. The temperature was 40° C. on admission and dropped to 37° C. in thirty hours and he was clinically better. The spinal fluid at that time contained 4,000 cells, all being polymorphonuclears. Up to the fifth hospital day, he had a low-grade fever between 37.5° C. and 38° C. On the sixth hospital day, a lumbar puncture showed 124 cells, 60 per cent of which were monocytes. He was discharged by release on the eighth hospital day, clinically cured.

PATIENT 16.—J. L. (Case 266775), a 38-year-old white female, entered the hospital acutely ill and somnolent, although she could be aroused. She complained of severe headache. The spinal fluid obtained on admission showed 4,900 cells, 94 per cent of which were polymorphonuclears. Culture and smears of the spinal fluid were positive for meningococci. She was given penicillin, 15,000 units every three hours for a total of 840,000 units. Clinically she made a fair response, although the temperature curve went up and down, becoming normal for a short time on the fifth hospital day, after which it remained close to 38° C. Up to and including the seventh hospital day, the patient complained repeatedly of a severe headache. The spinal fluid at this time contained 2,180 cells, 95 per cent being polymorphonuclears. The smears were negative, but the culture was positive. On the eighth hospital day, she was given sulfadiazine and her headache disappeared by the next day. On the ninth hospital day, the temperature was normal and remained unchanged until discharge.

PATIENT 17.—J. S. (Case 266904), a 38-year-old white male, was admitted in a wildly delirious condition. The spinal fluid contained 14,750 cells, all being polymorphonuclears. The smear and the culture were positive. On the second hospital day, the patient was quieter, but on the third hospital day he was alternately comatose and delirious, his condition becoming much worse. The spinal fluid at this time showed 2,000 cells. He had been given penicillin intramuscularly 15,000 units every three hours during this time and it was decided to continue the therapy. On the fifth hospital day he appeared no better. The spinal fluid contained 1,200 cells with many meningococci on direct smear. The treatment was changed to sulfadiazine and antitoxin after a total of 435,000 units of penicillin. The next day, which was the sixth hospital day, he was clinically improved, although somewhat disoriented. By the eighth hospital day, his temperature was normal, he was well oriented, and recovery was uneventful.

PATIENT 18.—R. B. (Case 267025), a 43-year-old Negro male, entered the hospital severely ill, toxic, semicomatose and delirious. The temperature was 38.8° C. on admission. There were 9,200 cells in the spinal fluid, all of which were polymorphonuclears and the smear and the culture were positive. He was given 15,000 units of penicillin intramuscularly every three hours. The temperature came down precipitously the next day, although the patient was worse clinically. On the third hospital day the temperature rose again to 39.9° C. Another spinal fluid was obtained and it contained 10,250 cells, all polymorphonuclears, but no organisms were seen. However, a culture of the spinal fluid was positive on the next day when the treatment was changed to sulfadiazine and antitoxin. A total of 240,000 units of penicillin had been given. The patient remained in a delirious and comatose state. The course was downhill and he died on the evening of the ninth hospital day following a generalized convulsion.

In these four cases, one patient bordered on a meningococcemia or very early meningitis, one was moderately ill, and two were very seriously ill.

Four patients with meningococcemia were treated with penicillin administered intramuscularly.

PATIENT 19.—A. F. (Case 264832), a 20-year-old white female, was a sister to a patient in the hospital with proved epidemic meningitis. The spinal fluid and the culture were negative. The blood culture was positive. The temperature on admission was 40.9° C. She was given 15,000 units penicillin every three hours for a total of 345,000 units intramuscularly. She improved rapidly and her temperature was normal within two days and remained thus thereafter. She was discharged by release on the sixth hospital day.

PATIENT 20.—G. L. (Case 267202), a 2½-year-old white female, was acutely ill on admission with a history of having been ill only twelve hours previously. She had numerous petechiae in the skin. The spinal fluid was negative. Blood culture and smears from the petechiae were positive for meningococci. Penicillin was given intramuscularly, 15,000 units every three hours for a total of 645,000 units. The response was excellent and within twelve hours after therapy was started. She was discharged on the seventh hospital day.

PATIENT 21.—V. E. (Case 267789), a 4-year-old white male, was admitted acutely ill, slightly delirious with a generalized petechial rash, stiff neck, and temperature of only 37.7° C. He became ill approximately eighteen hours before admission. The lumbar puncture was negative. Smears of the petechiae were positive for meningococci. Twenty thousand units of penicillin were given intramuscularly every three hours for a total of 700,000 units. The temperature became normal in twelve hours and he was discharged on the ninth hospital day.

PATIENT 5.—P. K. was the patient previously described. She had meningococcemia which progressed to meningitis despite the use of penicillin intrathecally.

SUMMARY

Twenty-one patients with proved meningococcal infections were treated with penicillin.

A. Fourteen of these patients had epidemic meningitis and were treated with penicillin intrathecally and intramuscularly. Eight patients responded satisfactorily; six did not respond so well to the doses administered.

B. Four patients ill with epidemic meningitis were treated with penicillin administered only intramuscularly. Of these, three did not respond too well to therapy and one died.

C. Four patients had meningococcemia and were treated with penicillin intramuscularly. Three recovered promptly. In one patient, the infection progressed to epidemic meningitis.

CONCLUSION

The daily intrathecal and frequent intramuscular administration of penicillin is a tedious procedure. To us the results are not of sufficient value to warrant its use as a form of treatment in epidemic meningitis when simpler and more effective methods are available.

REFERENCES

1. Rosenberg, David H., and Arling, P. A.: J. A. M. A. 125: 1011, 1944.
2. Davis, John H., Morrow, William J., and Toomey, John A.: J. PEDIAT. 26: 455, 1945.

USE OF AMINO ACIDS IN A CASE OF SEVERE SALMONELLA SCHOTTMUELLERI (PARATYPHOID B) INFECTION IN AN INFANT

MAJOR I. SEIDEMANN
MEDICAL CORPS, ARMY OF THE UNITED STATES

SALMONELLA schottmuelleri (paratyphoid B) infection in infants is not common. Except for reports of isolated cases, the literature on sporadic cases of infections due to Salmonella in infants is quite limited. A recent investigation reported by Neter[1] describes twenty cases of sporadic infections in infants. It took three years to collect these in a comparatively large-sized hospital in a large city. Of these twenty cases, only two proved to be of the schottmuelleri or paratyphoid type of infection. Investigations by Kauffman in Denmark, of Hormaeche in Uruguay, and Edwards, Shiff, Seligmann, Bornstein and Saphra in the United States, have added to the material knowledge of Salmonella infections in human beings. Most of the work on this disease has been done recently. Investigation of the older literature is very unsatisfactory. It is interesting to note that Finkelstein, the renowned European pediatrician of previous decades, stated that he had never observed a case of *S. schottmuelleri* infection in an infant under one year.[2] In general, this disease was not considered to be a serious one in children, although Neter, in the article previously referred to, described four fatalities in his report of twenty cases, and it was his opinion that the disease is not necessarily a benign one. However, Seligmann and Hertz[3] reported eight cases due to Salmonella in infants without fatalities. Numerous complications have been reported such as meningitis,[4] peritonitis,[5] and osteomyelitis,[6] as well as four cases with unusual complications described by Freedman[7] such as acute hydrops of the gall bladder, empyema, cavernous sinus thrombosis, and uremia (liver failure).

Treatment of the disease is not specific and has been more or less of the symptomatic and supportive type. It is the purpose of this paper to emphasize a phase of the supportive therapy by presenting a case report of a severe *S. schottmuelleri* infection in an infant, with recovery.

CASE REPORT

A 15-month-old male child, one of a set of paternal twins, premature at birth, was admitted on August 21, 1944, to an Army regional hospital in Georgia. Profuse diarrhea had been present for five days prior to admission, which was followed by vomiting the night before admission. He had retained little or no fluid for the past twenty-four hours. The skin was dry and the patient appeared somewhat emaciated. The turgor was poor and some hypertonus of the musculature was noted. The child had just returned with the parents from a trip to Mississippi and had been exposed to unusually hot sultry weather, and according to the father's history, had had some unpasteurized milk. Further physical examination revealed a listless, weak child, unable to take nourishment by mouth. The chest was clear, eyes, ears, nose and throat appeared normal; there was no rash present. Laboratory examinations re-

vealed 12,650 white blood cells of which only 37 per cent were polymorphonuclear and 63 per cent were lymphocytes. The hemoglobin was 13.5 Gm. The urine showed 4 plus albumin, occasional white blood cells and red blood cells as well as occasional hyaline and granular casts. Rectal temperature was 100° F., respirations were rapid and shallow. Fluids in the form of 250 c.c. of normal saline were administered intraperitoneally. Shortly after this small amounts of fluid were taken by mouth, but were soon vomited. Diarrhea continued to persist. The stools were watery and green. The first night was spent restlessly in spite of bromide sedation given by rectum. The following day the patient was started on a kaomagma-banana regime. The temperature rose to 103° F. Sulfadiazine therapy was begun but the general condition did not improve. On the third hospital day, August 23, a convulsion lasting three minutes occurred. In order to administer parenteral fluids, it was necessary to have the surgeon cut down on an ankle vein. A trocar was inserted and 2½ per cent glucose in normal saline was administered. Shortly thereafter a second convulsion occurred and it was then that pediatric consultation was requested in view of the lack of response to therapy as well as the progression of severity of symptoms.

Examination at this time showed the child to be in the midst of a convulsion; cyanosis and episthotonos were marked; exophthalmos and nuchal rigidity were present. All deep reflexes were exaggerated. There were definite signs of increasing meningoencephalopathy as a result of the severe toxicity. A transfusion of 100 c.c. of citrate of blood was given and resulted in only a slight immediate response. At this time the rationale of administering amino acids was considered in view of the explanation of a greater part of the toxicity being due to some liver damage. It is not uncommon to find on autopsy advanced liver damage in severe dyspepsia, especially in the so-called Finkelstein's intoxication. Consequently, after the transfusion, 30 c.c. of parenteral amino acids were added to 100 c.c. normal saline and given intravenously. There was no untoward effect and the response was dramatic. The child appeared much brighter within one-half hour after the administration of the amino acids, moved about more easily, reacted to sound and stimuli, and appeared to have a definite decrease in musculature hypertonus. The meningismus gradually subsided and the general toxic condition was greatly reduced. The stools soon after appeared less watery, became less frequent, and showed signs of a more normal appearance. In view of the dramatic improvement noticed after the administration of the amino acids, it was decided to repeat the procedure the following day and also attempt to give some amino acids by mouth with boiled water at intervals, which was somewhat successful. A formula of lactic acid milk was started also and well taken. All this time stools were being sent to the laboratory for culture, and on August 27, the seventh hospital day, a stool was reported positive for *S. schottmuelleri* and confirmed by agglutination with anti-Salmonella schottmuelleri serum. Spot agglutination tests for *S. schottmuelleri* were positive to 1 to 160 dilution on the ninth hospital day (second week of the illness). Stools were repeatedly positive for *S. schottmuelleri* again on the ninth hospital day. Verification of laboratory findings were made by agglutination with the anti serum of *S. schottmuelleri* as well as differential reaction with sugars. The blood agglutinated *S. schottmuelleri* serum up to 1 to 160 dilution. The stools and the urine became negative on September 5, the sixteenth hospital day, but the agglutination titer of the blood increased up to 1 to 320 dilution by this time.

The response to the second administration of parenteral amino acids was as dramatic as the first one. The patient showed sudden improvement. The stools practically became normal in appearance and reduced to normal frequency. The lactic acid formula was taken very well and by the eleventh hospital day Pablum, Jello, and custard were added to the diet, and later small amounts of ice cream were well tolerated. By the fifteenth day the stools were normal and regular diet was given. The baby was discharged as recovered on the nineteenth hospital day.

It is of interest to note that sulfaguanidine was tried in ⅓ Gm. doses every four hours for three days, but it failed to render the stools free of the infecting organism.

SUMMARY

1. The incidence of Salmonella infections in infants is not very high. The literature on the subject is not abundant, especially with specific reference to the schottmuelleri type of infection.

2. The disease, when found, was usually not considered to be a very severe one in infants, although various complications have been reported.

3. A case of severe infection with *S. schottmuelleri* in an 18-month-old child is presented.

4. The dramatic response attributed to the administration of parenteral amino acids as added supportive therapy was considered of general interest to warrant presentation of the case.

CONCLUSION

The value of amino acids as additional supportive therapy in the treatment of *S. schottmuelleri* infections in children, as well as other infectious diarrheas, appears to be deserving of consideration and should be further studied.

REFERENCES

1. Neter, E.: Am. J. Dis. Child. **68**: 312, 1944.
2. Brennemann's Practice of Pediatrics, Hagerstown, Md., 1942, W. F. Prior Company, Inc., vol. 2, ch. 31, p. 20.
3. Seligmann, E., and Hertz, J. J.: Ann. Int. Med. **20**: 743, 1944.
4. Aballi, A. A., Falcon, S., Sala Panisello, F., Curbelo, A., and Martinez Cruz, J. A.: Bol. Soc. Cubana de pediat. **9**: 123, 1937.
5. Bornstein, S., and Schwartz, H.: Am. J. M. Sc. **204**: 546, 1942.
6. Jetter, W. W.: Am. J. Dis. Child. **58**: 846, 1938.
7. Freedman, A.: Ohio State M. J. **319**: 418, 1943.

ACUTE GASTRIC ULCER WITH PERFORATION IN ONE OF PREMATURE TWINS

Report of a Case

Albert A. Rosenberg, M.D., and Mary H. Heath, M.D.
Poughkeepsie, N. Y.

BIRD, Limper, and Mayer[1] have collected the reported cases of peptic ulceration of the stomach and duodenum in infants and children. In 243 cases they found fifty-one infants in the age group from 15 days to 1 year, and of these only eight were gastric. To this group we wish to add another case which may be of particular interest because it occurred in one of premature homologous twins.

A. O. was born in the eighth month of gestation, reported to be homologous although the placenta was not examined microscopically, following an uneventful pregnancy and normal delivery, the first of homologous twin boys. His weight at birth was 3 pounds, 10 ounces. Physical examination was negative except for prematurity, and his condition was reported as good. For the first day the babies were fed glucose water at two hourly intervals and subsequently olac, from 2 to 4 oz. Their courses were parallel until the ninth day when A. O. vomited thick green mucus and his cry became listless. The following day his weight was 3 pounds, 1 ounce, as compared with 3 pounds, 4¾ ounces of the twin. From this time on he frequently refused feedings or retained them with difficulty, vomited his formula intermittently, became sallow and progressively weaker until death on the fifty-fifth day. His twin gained weight, grew stronger, and was discharged in good condition on the sixty-second day. Both received a formula of milk, water, and dextrimaltose after the twelfth day, thiamine chloride 75 mg. daily after the tenth day, and ascorbic acid, 25 mg. daily, after the thirty-third day. On the thirty-sixth day A. O. vomited a small amount of brownish fluid. At this time his hemoglobin was 15.8 Gm. Several days later vomiting became projectile. His stools were noted to be dark brown on the forty-fourth day and continued so until the end. They varied in number from none to three per day. Blood count about this time was as follows: hemoglobin, 10.3 Gm.; red cells, 2,380,000; color index, 1.18; white cells, 13,150; polymorphonuclears, 25 per cent; lymphocytes, 69 per cent; eosinophiles, 2.5 per cent; monocytes, 1 per cent; smudged cells, 2.5 per cent. Breast milk which had been given intermittently from the fifteenth day replaced the formula completely during the last two weeks. Roentgenograms taken on the forty-seventh day showed a large, gas-filled stomach with some gas in the small intestine. There was marked retention of barium in the stomach after three hours as compared with emptying time in the twin. The last week he was lavaged with soda bicarbonate, and gavage feedings of breast milk preceded by atropine were given. On the day preceding death it was noted that 30 c.c. of the lavage could not be returned. Throughout his course clyses were administered frequently and intramuscular blood was given three times. Aminoids, 1 teaspoon twice a day, was given the last three days. The temperature paralleled that of the twin until the forty-ninth day when it dropped to 95° F., and it varied from this to 100° F. until he expired. Weight two days before death was 4 pounds, 3 ounces, that of the twin 5 pounds, 5 ounces. At this time, however, the infant appeared malnourished and was edematous.

At autopsy, three hours post mortem, a large perforated gastric ulcer was found which involved about one-sixth of the gastric mucosa, similar grossly to the common peptic ulcer of adults. It was situated on the lesser curvature, 1 cm. from the pyloric valve, almost encircling the pylorus. The edges were rolled and the central ulcerated area depressed. Per-

From the Pediatric Service of Vassar Brothers Hospital.

foration had occurred at the proximal edge on the superoanterior aspect of the stomach near the liver. The gastric mucosa elsewhere was pale and somewhat thickened as was the muscularis of the stomach and of the pyloric valve. A plastic exudate was found over the surface of the liver, spleen, and along the descending colon and in the pelvis, and a small amount of purulent fluid was present in the abdominal cavity. The spleen appeared somewhat enlarged with a tense capsule. Other abdominal organs were not remarkable. In the thoracic cavity a few cubic centimeters of yellowish fluid was present on each side, that on the left containing some flecks of fibrinopurulent exudate. The lungs were reddened in their dependent portions but without consolidation. Excess fluid was found in the pericardial sac. There was edema throughout the areolar tissue in the mediastinum, mesentery, and retroperitoneal tissues, as well as in the lower extremities. Microscopic examination through the ulcer at the point of perforation showed an acute process with no attempt at repair. The edges of the perforation were necrotic, but there was little inflammatory reaction except for the exudate on the peritoneal surface.

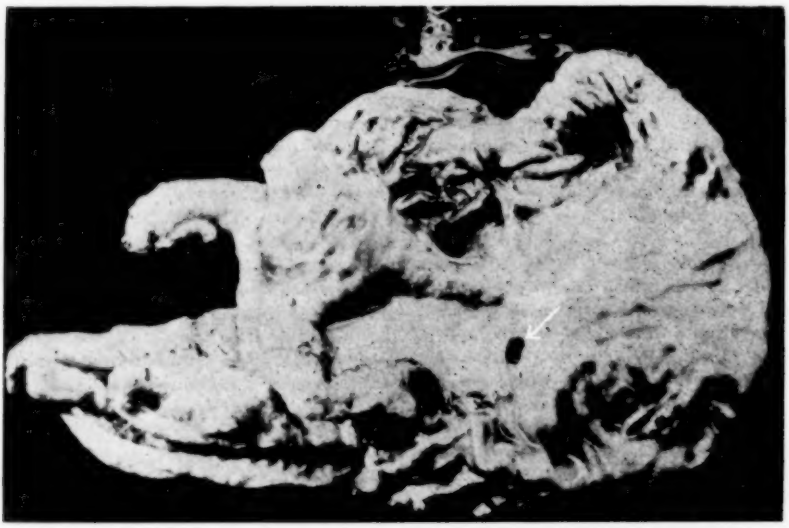


Fig. 1.—Stomach of infant after alcoholic fixation showing large ulceration on lesser curvature with site of perforation (marked by arrow) at proximal border.

COMMENT

The etiology in this case, as in the majority occurring in infants, is obscure. Predisposing factors mentioned by Guthrie[2] and others are lacking. Labor was uneventful and delivery normal. There were no congenital anomalies, nor did the infant have an exanthematous disease or suffer any injury or burns. The role of thiamine chloride and ascorbic acid as irritants seems to be excluded by their simultaneous administration to the twin. Smythe[3] has reported two cases occurring in premature infants. Our case also was a premature infant, but it is interesting to note that the twin on the same regime remained well. Crawford and Stewart[4] saw two cases complicating erythroblastosis fetalis. There was nothing in the history or in the post-mortem findings to suggest such a condition in this infant.

The first and most constant symptom was vomiting beginning on the ninth day. The brown stools and dark vomitus with the appearance of anemia may have indicated that there was bleeding dating probably from about three weeks before death, and on the day preceding death the perforation may have occurred as indicated by the failure to recover a quantity of the lavage fluid. At no time did the infant exhibit any sign of pain. He was considered to have pyloric stenosis and treatment was directed accordingly. Surgery seemed inadvisable because of the size of the infant and his condition. X-ray examination appeared to verify this diagnosis and failed to reveal the ulcer. In this connection Burdick[5] has pointed out the value of fluoroscopic examination in rendering a positive diagnosis. It would be difficult if the diagnosis had been made to imagine any medical treatment succeeding where breast milk and soda bicarbonate failed. Bird, Limper, and Mayer[1] have emphasized the possibility of surgery in ulcers in childhood and, in this case surgery might have offered the only hope of recovery.

REFERENCES

1. Bird, C. E., Limper, M. A., and Mayer, J. M.: Ann. Surg. 114: 526, 1941.
2. Guthrie, K.: Arch. Dis. Childhood 17: 82, 1942.
3. Smythe, F. W.: Am. J. Surg. 24: 818, 1934.
4. Crawford, R., Stewart, C. A.: Journal-Lancet 63: 131, 1943.
5. Burdick, W. F.: J. PEDIAT. 17: 654, 1940.

PAROXYSMAL TACHYCARDIA

Report of Two Cases in Infants

Edwin P. Scott, M.D., and Margaret A. Limper, M.D.
Louisville, Ky.

While cases of paroxysmal tachycardia in early infancy are being recognized with increasing frequency, comparatively few cases have been reported. We wish to add two cases, one with a fatal outcome, and one with recovery.

Case 1.—J. R., a 5-month-old white male infant was admitted to the Children's Free Hospital Sept. 28, 1942. According to the parents he was perfectly well up to ten days prior to admission, when he began to vomit. Intermittent vomiting continued up to hospitalization. The mother was told by several physicians that the infant's heart was "very fast" and that his "liver was enlarged."

Physical examination on admission revealed a well-developed and well-nourished white male infant in slight respiratory distress with a peculiar ashen gray color of the skin. The rate of the heart was extremely rapid, and respirations were shallow and 60 per minute. The liver was palpated three fingerbreadths below the right costal margin. The remainder of the physical examination was not remarkable.

The electrocardiogram revealed a supraventricular tachycardia with a rate of 250 per minute (Fig. 1, *A*).* There was marked passive congestion in both lung bases on the chest roentgenogram. A complete blood study showed a red blood cell count of 4,790,000 per cubic millimeter with hemoglobin of 94.1 per cent, and a white blod cell count of 13,500 per cubic millimeter with a differential of 43 per cent polymorphonuclear leucocytes, 50 per cent lymphocytes, and 7 per cent "stabs." A complete urinalysis was negative.

After a negative scratch test for quinine dihydrochloride, ½ grain was given intramuscularly, and no decrease in heart rate was noted. Two hours later 1 grain was given intravenously, and again no change could be demonstrated in the heart rate.

The following day, September 29, 2 grains of quinine dihydrochloride were given intravenously without immediate effect; however, when the infant was examined one-half hour later, the heart rate was 125 per minute. Soon the respirations became slower, the liver receded, and the ashen color of the skin disappeared.

The infant was observed for a period of five days and discharged on oral cocoa-quinine.

Numerous attempts were made for follow-up studies, but all were unsuccessful.

On the night of March 5, 1943, six months after the previous admission, the child was readmitted with a history of restlessness and intermittent vomiting of eight days' duration.

Physical examination revealed a well-developed, 11-month-old infant with an ashen gray color to the skin, respiratory rate of 48 per minute, rapid heart, and enlarged liver. The remainder of the physical examination was essentially negative.

Electrocardiogram† revealed paroxysmal ventricular tachycardia with a rate of 239 (Fig. 1, B).

After a negative skin test he was given 2 grains of quinine dihydrochloride intravenously, and a repeat electrocardiogram revealed no change. Six hours later 3 grains were given intravenously, and there was a sudden change of rhythm. Electrocardiogram made 90 seconds after injection revealed a rate of 165 with the QRS complex slurred and prolonged (Fig. 1, *C*).

From the Department of Pediatrics, University of Louisville School of Medicine.
*Prepared and interpreted by Dr. Emmet F. Horine.
†Prepared and interpreted by Dr. John Walker Moore.

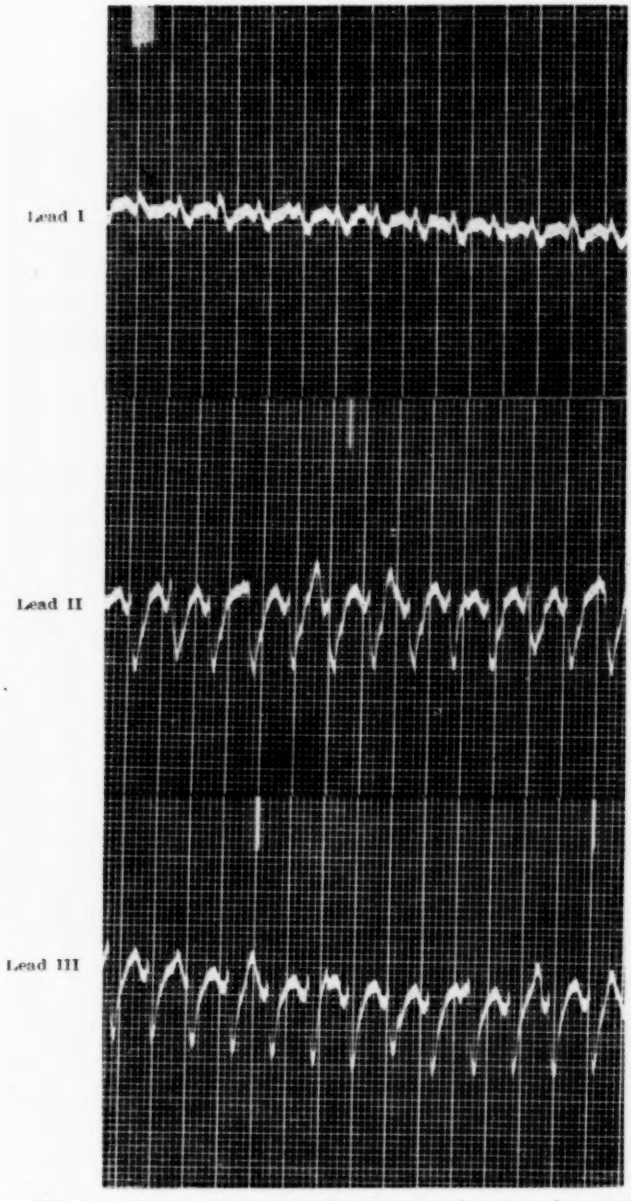


Fig. 1A.—Case 1. Supraventricular paroxysmal tachycardia. Rate 250.

Two hours after the injection of 3 grains of quinine dihydrochloride, the heart was again extremely rapid, with a rate of 239. In view of the return of the tachycardia, 4 grains of quinine dihydrochloride were given intravenously. About two minutes after injection the infant became restless and seemed to have laryngeal spasm. The heart continued to beat for several minutes, but the respirations could not be re-established, despite all emergency measures.

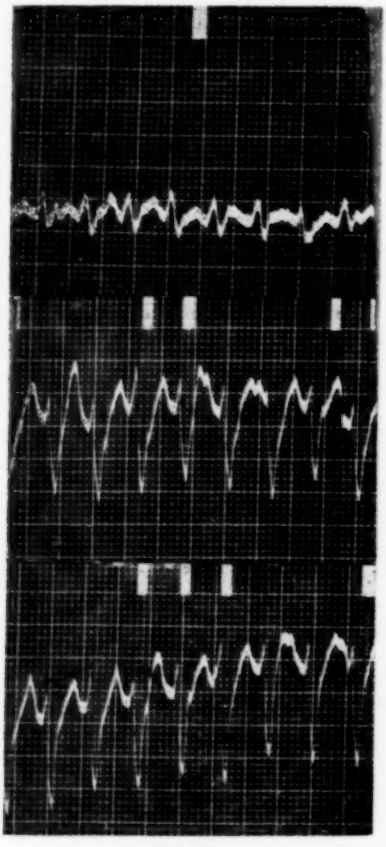


Fig. 1B.

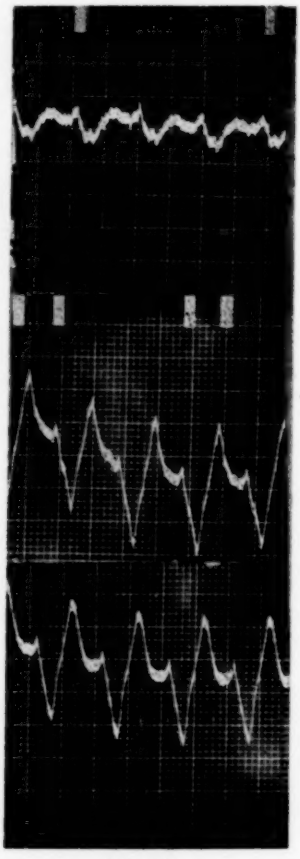


Fig. 1C.

Fig. 1B.—Case 1. Paroxysmal ventricular tachycardia. Rate 239.

Fig. 1C.—Case 1.—Ninety seconds after 3 grains of quinine dihydrochloride were given intravenously. Rate 165.

An electrocardiogram taken after respirations had ceased revealed a heart rate of 215. The QRS complex seemed to be longer on this tracing than on any of the previous records.

No autopsy was obtained.

CASE 2.—This 39-day-old male infant was admitted to Children's Hospital Feb. 10, 1944. The infant had been brought to see one of us (M. A. L.) for a routine examination. The heart rate was estimated to be above 200, paroxysmal tachycardia was suspected, and the infant was referred for electrocardiography. A supraventricular type of paroxysmal tachycardia, with a heart rate of 270, was found (Fig. 2, *A**). The infant was referred to the hospital.

*Prepared by Dr. Max L. Garon.

Past history revealed that the infant was full term, with a birth weight of 7 pounds, 9 ounces. He was the second child, and the parents and the older brother were healthy. His delivery had been normal. He was not examined by a pediatrician during the newborn period. He had developed impetigo during his hospital stay, and the mother had treated

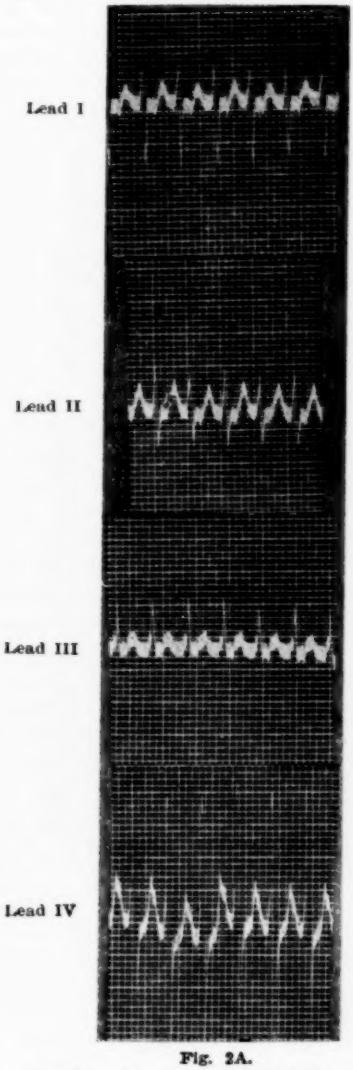


Fig. 2A.

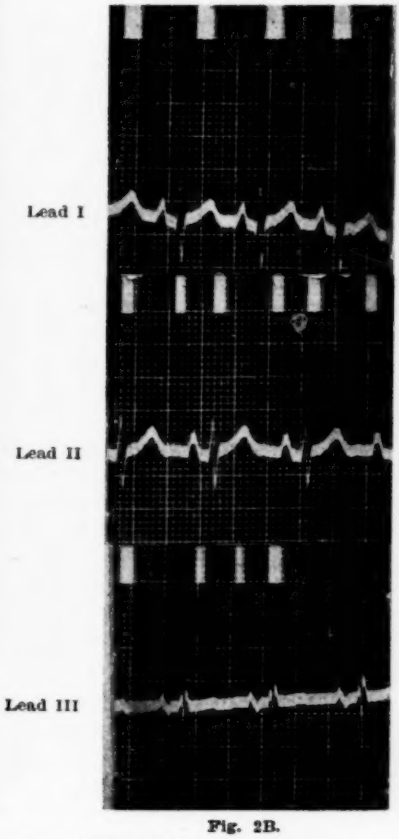


Fig. 2B.

Fig. 2A.—Case 2. Supraventricular paroxysmal tachycardia. Rate 270.
Fig. 2B.—Case 2. Rate 115.

the condition rather overenthusiastically by breaking the vesicles with an alcohol sponge, applying sulfathiazole powder, and changing the infant's clothing every four hours. Alcohol had also been used on the infant's breasts because of engorgement. The infant was receiving

a formula of evaporated milk, water, and corn syrup, supplemented with cod-liver oil and orange juice.

Physical examination revealed a well-developed and well-nourished 9-pound baby with an extremely rapid heart. The heart sounds were loud and booming; otherwise, the cardiac examination was not remarkable. On abdominal examination, the spleen could not be felt, and the liver was palpable but not enlarged. The temperature was 99.2° F., and the respirations 60 per minute. The infant's color was good at the time of admission to the hospital. (When seen in the office, he had an attack of hiccups and exhibited slight transient cyanosis.)

A complete blood study showed a red blood cell count of 3,860,000 per cubic millimeter, with a hemoglobin of 12.5 Gm. per 100 c.c. of blood, and a white blood count of 9,950 per cubic millimeter, with a differential of 62 per cent polymorphonuclear leucocytes, and 38 per cent lymphocytes.

On admission, the infant was given 1.5 grains (0.1 Gm.) of digifolin intramuscularly. Four hours after admission, the infant developed a cyanotic attack but responded readily to oxygen. About five hours after the digitalis had been given, the infant was examined and tachycardia was still present, although the rate seemed to be somewhat slower. Eight hours after admission the heart rate had dropped to 114 per minute. Following this, convalescence was uneventful. A routine electrocardiogram made Feb. 17, 1944, revealed a rate of 115 per minute. (Fig. 2, *B*.*) The infant was discharged February 18, and repeated examinations over a period of a year have shown no recurrence of the tachycardia.

COMMENT

The first patient (Case 1) was a critically ill infant on both of his admissions, and his second attack of paroxysmal tachycardia with congestive failure might have ended fatally under any circumstances. Paroxysmal tachycardia in Case 2 was observed more or less accidentally, before any symptoms or signs of congestive failure had appeared. In such cases patients occasionally recover without any therapy, as reported by Hubbard.[1] This author did point out that "digitalis or one of the digitalis preparations, when given in adequate amounts . . . has invariably been effective in stopping the tachycardia." This was true of eight of the nine cases reported by him, as well as of six of the nineteen cases reviewed by him. The case of Wegman and Egbert, which did not respond to digitalis, was found at autopsy to have rhabdomyosarcoma of the conducting system. Patients in five of the cases reviewed by Hubbard recovered without digitalis, and one of his own patients recovered spontaneously. He states that quinidine is of no value in paroxysmal tachycardia of early infancy; he also reported an extremely severe reaction in Case 6 of his series, in which mecholyl chloride was used.

Our experience bears out to some extent Hubbard's observations. It may be that if the difference between paroxysmal tachycardia of infants and that observed in adults had been appreciated when Case 1 was observed, that digitalis rather than quinine would have been employed, and a more favorable result obtained.

REFERENCE

1. Hubbard, John P.: Am. J. Dis. Child. 61: 687, 1941.

*Prepared and interpreted by Dr. John Walker Moore.

LEINER'S DISEASE FOLLOWED BY THE CELIAC SYNDROME

A Case Report

H. E. Thelander, M.D.
San Francisco, Calif.

SINCE attention again has been directed to the condition known as erythrodermia desquamativa (Leiner's disease) in infants, by Glaser and Markson,[1] it seems an opportune time to report the interesting occurrence of the celiac syndrome following recovery from Leiner's disease in my previously reported case.[2]

In a review of the literature on Leiner's disease, no other case with this combination of pathology was found, and in Andersen's[3] article with its comprehensive review of cystic fibrosis of the pancreas and celiac disease there is no reference to any cases associated with Leiner's disease. Even a single instance, however, may add some pertinent piece in the mosaic of information that is bing pieced together to complete the picture of Leiner's disease.

CASE REPORT

(Continued from previous article[2])

A. B. at the time of the 1937 report was 8 months of age and weighed 18 pounds. Her hemoglobin, which had been as low as 46 per cent, was 70 per cent. Her skin and hair were normal, and she was on the regular diet for her age with the addition of synthetic vitamin C and iron, the former because of a tendency to orange allergy and the latter because of anemia.

Shortly after the original report, the child was taken out of town for a family holiday. Heat and dust storms were encountered and the child developed anorexia which was followed by a persistent diarrhea, refractory to ordinary palliative measures. Upon return from this trip, the patient weighed 14 pounds, 12 ounces, which represented a loss of 3½ pounds in one month. She presented a picture of extreme emaciation and dehydration but was afebrile and had no localized pathology. After a short period of observation, a tentative diagnosis of celiac disease was made; this was confirmed by subsequent stool studies, the clinical picture, and the course of the illness. She was given one transfusion of 160 c.c. whole blood and placed on a celiac regime.

From June 25, 1937, to Dec. 17, 1937, a period of six months, her weight remained practically stationary varying a few ounces up or down at each weighing. She was irritable, wakeful, and extremely unhappy. The stools were characteristically light-colored, foamy, and voluminous. She was emaciated with a large distended, doughy abdomen, flat, sagging buttocks, and slender, fragile looking legs. Her hair was very fine in texture, scant, and slow growing.

Her diet, which at first consisted of peptonized skim milk, bananas, and concentrated vitamins C, A and D, and the B complex, was gradually increased as her stools and general condition warranted it. The additions were made in the following order: cottage cheese made from skim milk, scraped beef, Jello, and gelatin, egg white; these were followed by the cautious addition of selected puréed fruits, and vegetables and, lastly, by carbohydrates and fats. Honey was tolerated better than other sugars and starches. The vitamin B preparations of 1937 were not as palatable as the present ones, but the mother was so convinced that the child was better when taking them that in spite of difficulties of administration, they were given regularly.

When examined on Jan. 10, 1938, the patient showed her first satisfactory gain and general improvement. This change had been preceded by a change for the better in disposition and general comfort, as well as in the character of the stools. From this time on she showed a consistent improvement which is unusual in this condition and can undoubtedly be attributed to the splendid and intelligent cooperation of the parents. The mother prepared every meal and with very few exceptions was present for the feeding. The child was guarded against infection with an almost superhuman diligence.

In 1938, at the age of 21 months, the patient weighed 24 pounds, 5 ounces, a gain of 8 pounds, 12 ounces in six months. Her appearance had improved markedly although her abdomen remained distended. She required careful watching of her diet as even a slight variation would precipitate a return of the irritable disposition, discomfort, and abnormal stools. It was probably because the mother never ignored these warning signs that the child at no time had a true relapse following the initial disease, a rather remarkable fact.

In June, 1939, two years after onset, A. B. weighed 34 pounds and was 37 inches tall. In 1940, at the age of 3 years, 6 months, she was still taking four bananas daily, skim milk, scraped beef, egg in limited quantities, carefully selected and prepared fruits and vegetables, a very restricted amount of butter, and the vitamins C, A and D, and the B complex.

In June, 1941, her weight was 44½ pounds; her height, 44½ inches; and her width, 18 cm., which compared favorably with the normal. Her teeth had erupted normally and were normal in appearance. She had had the routine immunization procedures, she had had an occasional cold, all of which she took in stride. Her diet was still limited in carbohydrates and fats and she showed discomfort when Vitamin B was omitted from her daily diet.

When 5 years of age the family left the city and I have not seen the patient since. A report from the parents in 1944, when the girl was 8 years of age, stated that she was tall and slender but in excellent health, she was doing well at school, and she was on a normal diet with only slight precaution taken in the use of fats and carbohydrates.

COMMENTS

This case is reported because of the occurrence in the same patient in rapid sequence of two poorly understood syndromes. Although I fully appreciate that this may be mere coincidence, nevertheless, there are a few pertinent facts that deserve cognizance. Among the many therapeutic measures suggested by various authors for Leiner's disease is that of a diet low in carbohydrates and fats; Glaser reports pathologic findings in the liver and pancreas in his cases; and the present knowledge of the relationship between deficiencies, causal or resultant pathology, intestinal and skin conditions is meager.

REFERENCES

1. Glaser, Kurt, and Markson, Simpson M.: J. PEDIAT. 26: 367, 1945.
2. Thelander, H. E.: Arch. Pediat. 54: 496, 1937.
3. Andersen, Dorothy H.: Am. J. Dis. Child. 56: 344, 1938.

American Academy of Pediatrics

Proceedings

Meeting of Members of Study Group and Committee on Study of Child-Health Services

A meeting of the members of the Study Group and the Committee on Study of Child-Health Services of the American Academy of Pediatrics was held at the Palmer House, Chicago, on Oct. 20, 1945. There were present Drs. Warren R. Sisson, Joseph S. Wall, Borden Veeder, Joseph I. Linde, Allan M. Butler, Edgar E. Martmer, Clifford G. Grulee, Henry Helmholz, Lee Forrest Hill, Harvey F. Garrison, Katherine Bain, James L. Wilson, Charles L. Williams, Jr., Joseph Lachman, and Mr. Rollo Britten of the U. S. Public Health Service, and Mrs. Elizabeth E. Boles of the Hospital Commission.

The following subjects were discussed at the two sessions which lasted from 9 A.M. to 4:30 P.M.:

Educational Study
Finances of the study, including visitations to various Foundations
Selection of an executive secretary or director of the study, representing the American Academy of Pediatrics
Presentation of proposed schedules by Drs. Bain and Williams of the Technical Staff
Cooperation of the Hospital Commission with the Academy study
Report of the plans for the pilot study in North Carolina, under the direction of Dr. Lachman, who has been working in the public health service in Kentucky
Report of the visit by Drs. Bain and Sisson to Roaring Gap to meet the members of the North Carolina Pediatric Society
General discussion of the study in reference to pending federal legislation
Selection of a qualified person to cover the so-called public relations activities of the study
Presentation of the committee's activities to the Academy at the meeting in Detroit

Dr. Wilson presented a detailed preliminary schedule for the educational study. He defined the purpose and scope of the study as follows: "To get detailed and, as far as possible, comparable information as to what is taught regarding normal physical and mental development and the illnesses of children in each of the medical schools in the country, this to relate specifically to: (1) undergraduate instruction; (2) graduate instruction. (This may be covered adequately by the hospital intern and resident survey.) Scope: We will define the teaching of pediatrics to include all the information that a pediatrician acting as the family doctor would need to know about infants and children. The survey would, therefore, collect information about the teaching of surgical, otolaryngological, ophthalmological, orthopedic, etc., conditions in children, although not the most technical part of the treatment." Two possibilities for carrying out the study were outlined by Dr. Wilson as follows: "1. A full-time man to take two years to visit personally every medical school. 2. The division of the 70 odd medical schools into, let us say, 7 groups and a crew of 7 men appointed, each to visit one group within a year. The first arrangement is simpler and would give us a more unified basis for comparable opinions and would centralize the clinical work, but has the disadvantage of almost necessarily requiring the time of either a retired teacher of pediatrics or a young man not of national reputation. The second arrangement seems more practical but certainly might result in ten different base lines on which to compare schools. This might be partially offset by careful final summary." Dr. Helmholz

made the following comment concerning the proposed educational study: "I think the thing that we want to emphasize is the education of the men in the medical schools. We as a group of pediatricians would want to think of the education of the pediatrician. In our whole program what we are trying to do is to try to raise the level of what the general practitioner knows about pediatrics. I think we have to emphasize that part of pediatric education not the education of pediatricians, which after all we have pretty well taken care of. There are good schools, better schools, and very poor schools with regard to the actual training of pediatricians. Here we are further raising the level of all men who are practicing medicine. Then I think the relationship of the budget to the course given is pretty much stating in another way what you have said that one institution can give two hundred hours and another cannot give seventy-five because they have not the wherewithal to do it. Along that line we might be able to say what is needed, certain essentials that we cannot get along without. We ought to be able to set a minimum which is necessary to give adequate pediatric training to the man who is going out in general practice. That is something that we could do, not to try to level off at any level, but set a certain minimum that we cannot get along without. If a man has an outpatient department, ten or fifteen beds and no newly born service, you know very well how hard he is trying with a budget of $2,000 and he cannot adequately teach those students."

In regard to the financial aid for the over-all study, preliminary reports were made by Dr. Wall, Dr. Helmholz, and Dr. Sisson. The National Foundation for Infantile Paralysis has been visited and we are now awaiting a further opportunity to present the plans for the Academy study. The Foundation seemed interested and we are hopeful that they will make a grant. The Rockefeller Foundation has also been approached and our request is still under advisement. We have asked the Rockefeller Foundation if they would be interested to give us the advantage of their experience and also their financial help in promoting the educational study under Dr. Wilson's guidance. In this connection, Dr. Wilson pointed out that the most valuable information that will come out of the educational study cannot be put down on paper. "It is the attitude of the teachers that is most important." The Kellogg Foundation has also been approached for funds. The chairman called attention to the fact that we have spent $835.96 to date and that the assets of the fund are approximately $15,000.00 which includes the generous check of $8,000.00 from the Mead Johnson and Company.

It was moved by Dr. Veeder that Drs. Sisson, Wall, and Helmholz be empowered to act as an executive committee in the interim between committee meetings. This motion was seconded and carried.

The chairman then discussed the various individuals who had been proposed and interviewed as possible condidates for the position of director of the study. It was the unanimous consensus of the group that Colonel John P. Hubbard be invited to take the position and Dr. Helmholz was instructed to send him a telegram to this effect. The meeting was then turned over to the discussion of the various schedules. In order to give an idea of the extent of this phase of the study, the following outline of schedules is listed:

I. Hospitals, sanatoriums, and related institutions
   Pediatric hospitals, general hospitals and other hospitals with maternity facilities
   Special hospitals admitting children: nervous and mental hospitals, and institutions for the feeble-minded; tuberculosis hospitals, sanatoriums and preventoriums; convalescent hospitals, contagious hospitals, orthopedic hospitals
II. Health Services available on a county or city basis:
   Child health conferences; school health services; mental hygiene services; public health nursing services
III. Personnel engaged in private practice.
   Physicians other than pediatricians; pediatricians; dentists
IV. Training facilities in pediatrics
   Pediatric departments in medical schools; postgraduate training for doctors; postgraduate training for nurses

Mrs. Elizabeth E. Boles of the Hospital Commission was present at the meeting and gave valuable suggestions in regard to how we could take advantage of the schedules now being used by them.

It should be stated that Mr. Britten of the U. S. Public Health Service made constant suggestions from his vast experience in statistical investigations which added greatly to the discussion.

The chairman gave a brief report of his visit with Dr. Bain to Roaring Gap, N. C., to meet the pediatricians at their annual medical meeting on September 8. The North Carolina pediatricians were most hospitable and we left with the feeling that Dr. London, the President of the Society, would be unquestionably successful in engaging the complete cooperation of the pediatricians of the state.

Dr. Lachman then presented in detail the plans for carrying out the pilot study in North Carolina. The time schedule which Dr. Lachman has developed for this study should bring the work to a successful conclusion by the middle of December. Dr. Lachman pointed out that he felt he could, by personal visitations to the pediatricians, make it clear that our study is not a part of the Pepper bill, which seemed to be a prevalent opinion in certain parts of the country. He emphasized that the purpose of the study is to discover the extent of medical facilities in order that physicians may adapt them to their local needs. At this point, Dr. Butler made a similar remark: "I do not see why we cannot emphasize that this is a study by doctors for doctors that will bring to doctors the information they need to carry on their work."

The committee next discussed the possibility of obtaining the services of a person qualified to present the plans and activities of the committee to the medical profession and to the public at large. Dr. Veeder emphasized the willingness of the editors of the JOURNAL OF PEDIATRICS to include reports and editorial comments concerning the committee's proceedings. It was the conclusion of the group that we should be very careful in the selection of the person for the position of public relations and it was resolved that the matter should be given more consideration before final action was taken. In connection with the question of publicity, it seemed very desirable to the committee to have an opportunity to present the agenda of the Committee on Study of Child-Health Services at the Detroit meeting of the Academy.

The committee decided to reconvene at the time of the Academy meeting in Detroit.

Academy News

The deaths of the following Fellows have been reported to the JOURNAL:

Dr. Robert G. McAliley of Atlanta, Ga., at the Walter Reed Hospital, Sept. 15, 1945.

Dr. Archibald D. Smith, Garden City, New York, Nov. 23, 1945 (Emeritus Fellow).

Dr. Manning C. Field, Brooklyn, N. Y.

The Social Aspects of Medicine

Suggestions for the discussion on social planning at the approaching Academy meeting in January:

1. Let us not waste time saying that physicians are superior ethically to other occupational groups. Physicians by and large probably do not differ much from the general run of human beings. It is much safer for us to assume that anyway.

2. Let us not waste time, either, in saying how enlightened pediatricians are. The pediatricians have been most forward in the practice of preventive medicine, but that development was a corollary to our work and need not go to our heads.

3. Also let us not waste time in pointing to achievements in medicine of the last twenty years as if they implied that the public need have no voice in determining medical care. The achievements in medicine merely parallel those in chemistry, physics, and mathematics; they are just part of a general advance in science. The essential point is that the advances in medicine have far outstripped their social applications and have created new needs and possibilities.

4. In our discussions let us keep ever in mind that both sides are actuated by a common desire to make medical care adequate. One side is approaching the problem from the point of view of the recipient and tends to see things in a Utopian luster and perhaps does not think enough in terms of practicalities. The other, approaching the problem from the point of view of the purveyor of medical care, tends to think too much in terms of administrative technique and perchance does not see in large enough perspective the objects to be gained. There should be no ground for emotion. The differences are just differences of judgment.

5. In all our discussions let us think primarily what is best for the children and, no matter what comes up, never lose sight of that goal. Physicians are the providers and ministers of medical care. Proposals for improved care are not designed for their comfort or emolument but for the comfort and welfare of the people. The great mistake which some medical groups are making is to think primarily of themselves, as if the medical profession formed a great trade union and the important thing was not to give up any advantage or to make any change until forced by pressure. Let us not allow our own images to obscure our view.

6. Whatever we do at the approaching meeting, let us offer something constructive and not commit the error of tearing to pieces plans for improved medical care without proposing any alternative beyond the preservation of the status quo. If any one single fact is clear, it is that the status quo is not enough to satisfy the public demand. Further, not only must we develop constructive proposals, but they must be sounder and better than others so that they will be accepted on their inherent merits. Proposing something wiser and better than the present bills offer is the only way by which these bills or their children or cousins can be defeated. The President in his recent message to Congress mentioned among the "certain rights which ought to be assured to every American citizen" "the right to adequate medical care and the opportunities to achieve and enjoy good health." Any recommendation endorsed by the Academy of Pediatrics must be big enough to have that end in view.

7. In our thinking and recommendations let us not hesitate to strike out for ourselves. There is a great opportunity at the present time for medical leadership and leadership can only be accomplished by independent thought and action. The present opening for wise action is the greatest that pediatricians have ever had.

E. A. Park.

COMMUNICATIONS

December 7, 1945.

In the early fall Dr. Harold Root of Waterbury, Connecticut, wrote me a letter for my column. Being a good friend of Dr. Root I took the liberty of criticizing it. Root wrote a vigorous defense of his position. I liked his letter of defense so much better than the original that I am publishing it. The original letter was a formal statement; the latter has all the advantages of informality, spontaneity, and directness and gives the clearer view of the thinking of the author.

E. A. PARK.

---

103 North Main St.,
Waterbury 14, Conn.

Dr. Edwards A. Park,
The Johns Hopkins Hospital,
Baltimore 5, Maryland
Dear Dr. Park:

I was very much interested and a little disappointed in your letter of November seventh. My experience has been that the majority of full-time physicians in teaching medical centers are in sympathy with government control of medicine; and I did not expect that our ideas on this subject would be identical.

We are all in agreement on one thing, good medical care at reasonable cost for all individuals, the question of method is where we differ.

The rank and file of doctors who do the hard work, night calls, treatment in the homes under anything but ideal conditions, the grueling twenty-four hour a day seven days a week on call sort of a job, are unfortunately not all idealists and do not always do exactly the right thing at the right time. They do, however, do a fairly efficient job in the majority of instances. It is the ones who do not do such a good job and cannot make a decent living, who lower the standards of care in any plan, and who gravitate into the Armed Services and particularly the Veterans Administration. I know several in Waterbury and Connecticut who did so after the last war and others who are headed that way now. This is not so apt to be true in the State and Public Health Services. Most of the applications are from this type person, but they are well screened before getting the job. I have served on the Connecticut examining board, and know.

Do you know who goes to the refresher courses, clinical congresses, and educational medical gatherings? Usually the same old crowd, those physicians who need the instruction least, but are determined to keep up as best they can with the newer developments. I am afraid that under government direction with fixed salaries, and fixed routine with the competitive factor removed, the desire to do the best work and to keep up with the latest advances might be further retarded.

This is demonstrated by any number of instances which I can quote you from personal knowledge of working conditions in the Army. The reluctance of the medical officers to do anything out of the ordinary routine or after hours for even the alleviation of the sick. Of course I am speaking of the rank and file, not the higher type medical officer. The rank and file are the ones who will bear the burden of any government program, however. This type person is also the one who doesn't care to take the trouble to keep abreast of the times.

Another type of government inefficiency: Two hospitals in England twenty-five miles apart. One of a certain type calling for a comparatively small staff, the other a different type calling for a larger staff. The smaller hospital consistently gets at least twice as many war casualties as the larger. The staff here works almost continuously trying to

keep up with the rush, whereas the staff in the larger hospital sits around a great deal of the time. Can anything be done to correct this? No, according to the Army officials. Rules are rules and the staffs must do the best they can under the circumstances. This is the type of inefficiency I am afraid of under government control.

Many of us attend well child conferences run by the city or State. In a discussion with some of the best pediatricians in the State a short time ago, we were all regretting that we could not do as good work at these conferences as in our offices due to the fact that we have to see so many patients in such a short time. This condition, I think you will find, applies in most, if not all, such clinics. You may say this is better than nothing. True, but not better if made nationwide under government control than facilities such as well child conferences, maternal clinics, dispensaries, T. B. clinics, etc., etc., that are now available to everyone in the States with good health programs. Those States without good programs should of course have facilities provided, as they will be under the Hill-Burton bill which is receiving the backing of organized medicine. My point is that where need has been demonstrated, the States should expand the existing services to meet those needs with government assistance where necessary.

For instance the Pepper bill calls for care of all mothers, regardless of race, creed, or financial status, all children under twenty-one, all crippled children, etc., etc., and yet appropriates only $100,000,000.00 for this program. Why not see what needs are demonstrated in the survey of the postwar planning committee of the Academy of Pediatrics and then propose legislation to meet those needs?

I will attempt to answer your criticisms point by point.

1. My reason for listing some of the accomplishments of medicine up to the present time was to show that a great deal has been and is being accomplished without government control of medicine. There was no implication of perfection. Just a record to be proud of. Perhaps it should be omitted.

2. There is a panel system in England, Australia, New Zealand, Canada, and most of the other government managed plans. The plan in England is admittedly unsatisfactory by all parties, government, doctors, and people. The British Medical Society has several times endorsed the plan in the past twenty years, but always suggests improvements, and points out the weaknesses in the plan. There has been little improvement since 1911. Thus far, hospitalization has not been included, nor specialist services, nor care of dependents. The doctors are allowed an unlimited number of patients on their panels which leads to rush medicine, and poor care.

In New Zealand the plan is more inclusive. It started on a fee per panel patient per year basis. The fee was small and the patients demanding in their care. The doctors were very dissatisfied. A change was made to fee per visit, then to a plan where the patient paid part of the fee. The paper work and dissatisfaction of both doctor and patient has mounted steadily particularly recently, and the government has not enough appropriation to meet the cost. The plan is, therefore, near collapse. The care of natives is not included in the plan. There is no provision for the indigent in either of these plans.

In Sweden there is a very satisfactory government plan, government owned hospitals, etc. Nearly all costs paid by the government, not an insurance system.

In Norway and Denmark with a homogeneous type population a satisfactory compulsory insurance system had been worked out. Almost complete medical, dental, and hospital care. It is interesting to note that the individual pays 0.6 of the fee for medical care, government 0.1, employer 0.3.

3. My letter was written to express some reasons why I feel that the lay person would not get as good medical care at reasonable cost under the Murray-Wagner-Dingell bill as by the combination of voluntary prepaid medical plans, plus hospital insurance plans plus expansion of State Health Department Services as need is demonstrated with government assistance where needed, plus plans for care of the indigent by the community or State again with government assistance where needed.

There are already 18,800,000 members of the prepayment hospital plans and it is only beginning in some states. Connecticut has well over one-fourth of its population enrolled in this plan and it is growing rapidly each month. Prepaid medical plans are just starting in most states and will undoubtedly help solve the problem of good reasonable medical care.

I realize that doctors are servants of the public, perhaps even better than you, and that the majority of the people will get what they want or think they want. Having corresponded at some length with the editor of the C.I.O. periodical in this area, I also know something of its goal as to medical care and sympathize with it.

Medical care in some States, notably in Connecticut, is rather efficient and becoming more so all the time as the State and other health programs develop according to need. There are large areas where there are no doctors. Are you or am I going to these areas if government takes control? Who, even though subsidized, is going to these thinly populated areas where practice is so spotty?

There is a very efficient mechanism in many communities whereby the indigent get good medical care of which I could tell you the details. Of course in others there is none. What about Maryland's new plan as published in the October JOURNAL OF PEDIATRICS? What about many other plans in the developmental stage? Would it be any better under governmental control with the usual red tape involved? Good dental care for all children would be ideal and I am all for it. Many States are developing or have developed excellent dental programs. Here again by all means government aid to the States who need assistance to attain this goal. The same applies to medical centers where needed. I sincerely hope the medical schools can and will take over the task of keeping up the education of the doctors in a community, but how are you going to get the doctors, rank and file, to go and be educated?

My letter may be destructive as far as the Murray-Wagner-Dingell bill is concerned, but did you notice the program which I suggested on the last page of my letter and have repeated in this letter? I grant that doctors have been slow to awake and even slower to propose cures for the medical ills of the world. I know that hundreds of them now are devoting a great deal of time to the study of this question and are trying to work out a solution which will react more to the benefit of the public than government control. Some of us still think this can be done. I believe that the government should set standards for care and see that they are carried out by the States with financial assistance by the government where needed.

We may both be wrong, but at least we are thinking toward the same ends.

Sincerely yours,

J. HAROLD ROOT, M.D.

November 15, 1945

November 27, 1945

Honorable Claude Pepper, Chairman
Subcommittee on Wartime Health and Education
Committee on Education and Labor
United States Senate
Washington, D. C.

Sir:

I have your letter of October 24, 1945, inviting me to comment on your bill S-1318 concerning maternal and child welfare in this country. I am taking your invitation literally. I write as a professional teacher of pediatrics and as one who receives a very minor part of his income from private practice.

The purpose of the bill and the ends desired to be reached, seem to me so admirable as to need no defense or comment. Any differences of opinion must be about a means to these ends.

I do not believe that the present members of the medical profession would be able to do as good a job as they are now doing if bill S-1318 were put into effect with no more controls on the rate of its actual implementation than are now provided. The bill as written, like other bills I have seen and particularly the all-inclusive Murray-Wagner-Dingell bill, is based on an idea which seems almost naive to an actual practitioner of medicine as myself, that is, that most of the troubles of mind and body that we see so pathetically prevalent in our children are due to such lack of financial resources by parents that they are unable to pay for proper medical and hospital care. Regardless of how much money is appropriated by Congress or State legislators or by philanthropic organizations, it can be said without qualification that the sort of medical care given to our people in the next twenty years is being determined now by what is being done in our medical schools and in graduate teaching hospitals.

A general tax supported medical payment scheme would certainly enable some children to get medical care that otherwise they would not receive. It seems to me, however, that there is far too great emphasis on this aspect of the problem and that a vastly greater part of the difficulties that result in the physical and mental defects of children are due to more profound and important factors which are open to direct solution and that steps toward their solution should be taken before a medical prepayment project on a national basis is undertaken.

One of these fundamental difficulties is the obvious one that the science of medicine has not progressed to the point where much effectively can be done about a great many of the ills and complaints to which man is subject, such as many of the most striking ones obvious to the man in the street, as arthritis and paralysis. This, of course, is in itself no argument against your proposals as one should make full use of what medical knowledge exists at present, but it is important for proper orientation in comparing what could be accomplished by a great extension of the present habits of medical practice, as would be accomplished by effects of bill S-1318, versus research to directly attack the basic defects in medical knowledge. Another problem that must be clearly analyzed is that states of nutrition and physical environment dependent upon intelligence and economic status have great bearing on health, so much so that the figures that you quote in your speech introducing the Pepper bill when you compare the infant mortality of Connecticut and New Mexico reflect the influence of a great many more factors than the amount of medical services available in the two states.

Any critical and sophisticated observer of the actual practice of medicine would agree with me that by far the greatest obstruction in the path to universal good health of children, in addition to the fundamental lack of medical knowledge which can be met only by medical research, is a great shortage of doctors, a great defect in the distribution of doctors, and, most important, a great defect in the quality and training of the doctors that we do have. These difficulties are immeasurably more important than lack of funds to pay for medical care. In my opinion a large proportion of the practicing physicians in this country are unable to wisely or skillfully diagnose and care for ailing infants, so that in many instances their attention can and does result in more harm than good. The crying need in this country is for more doctors and for better doctors, skilled in the care of infants and children. Undoubtedly the same thing can be said in other fields of medicine. In this bill there is a brief, almost casual mention of research and education. No clear-cut program is proposed, or precise allocation of funds made for these purposes. No assurance seems given that even the vague suggestions made regarding aid to education and research would be adequately carried out by state organizations who may be more interested in giving direct aid to individual voters. The total of the budgets of all the medical schools in this country is now less than forty million dollars, an amount trivial compared to that proposed to be appropriated for the purposes of bill S-1318. During one twelve month period the cost of the EMIC program alone, a program offered by the government without proof of need, as a gracious and justified gratuity to the members of our Armed Forces,

was about one and one-half times as great as the total budgets of all the medical schools in the country. Graduate education, by which I mean training of physicians as interns and residents after receiving their M.D. degree, is pathetically inadequate. Only a small proportion of the hospitals in this country are suitable for such training. The demand for good training opportunities was immensely greater than the supply even before the great aggravation of this difficulty by the return of medical veterans from the war. It seems to me therefore, almost absurd to indulge in this great preoccupation with techniques of distribution of medical care rather than to concentrate on the improvement of the quality and quantity of physicians. The future of medical research as well as medical education is entirely bound up in the facilities and ideals of our medical schools, yet most schools are operated on financial shoestrings with inadequate staffs and with research supported by temporary gratuities from drug companies or by foundations who want to initiate studies from which acknowledging papers can be made in one or two years.

The success or failure of the program outlined in the bill in meeting the desirable ends will obviously depend to a great extent on details of administration. All these are left for decision, apparently at the state level. It seems to me that unless many of these details can be boldly and courageously faced by Congress before being passed on to the state, it is obvious that enormous difficulties will rapidly arise about such a widely sweeping project, difficulties which will soon end in confusion and acrimonious arguments and strife between public health administrators and the medical profession. This might easily be tolerated if we were sure that the final results achieved would be good. It would seem that an almost inevitable leveling of fees to physicians would take place, in itself unimportant unless it resulted, as I strongly believe it would, in a failure of stimulation of the better trained practitioners and encouragement for the rapid production of the more poorly trained practitioner. In the last fifteen years there has been a rapid increase in the number of men practicing the specialty of pediatrics. These physicians spend a minimum of two years in a pediatric training center and then devote themselves wholly to practice limited to infants and children. In the last decade and a half they have decidedly raised the type of medical care that the children in this country receive. Although at present they do not care for more than 10 per cent of our child population, the number of such men training themselves for certification by their Board was increasing year by year at a rapidly accelerating rate up to the time of the curtailment of all such training by the war. You should understand that these men practiced their "specialty" not in a consultative capacity for wealthy and especially puzzling patients, but much more as general practitioners particularly trained to give continuous and complete care to their young patients. The use of these men, therefore, in a position only as consultants with a fee devised for that purpose is in no way in line with the natural and gratifying development of pediatrics. Such schemes as a national insurance plan, adopted at this time with such a small proportion of men with special training available would greatly handicap the development of more pediatricians unless a special fee for them could be devised, and such an arrangement would be indeed extremely difficult to administer as it has proved in other less extensive programs. Almost the same obstruction would arise to the development of more trained obstetricians, not to be used only in matters of emergency or consultation, but for the routine care of the average woman. Unless far more particularized organization of the administration of the bill were planned than appears at present, and unless some of the most controversial problems of medical economics are first solved in a manner that I am not wise enough myself to plan, I firmly believe that the fine purposes of the bill will be defeated by a nationwide increase in the quantity with great decrease in the quality of medical care given. I do not believe the public, and much less the medical profession, is yet able, or will be in the next few years, to use wisely the enormous funds that would be so soon available without such waste as to soon disgust our voters. Although certain states with population in the lowest economic group might attract more needed physicians, it seems to me there is little provision in the bill for means to attract the best trained instead of the worst trained practitioners.

A detail of the bill relatively unimportant might still be mentioned. S-1318 makes a distinction between sick children and crippled children. This distinction is common in state as well as national medical service programs and seems to be carried along in the legislative mind with little reason. The classification seems to me highly artificial since no one knows exactly what a "crippled" child is. Attempts to make such distinction causes overemphasis on the sort of crippling that can be seen by casual lay observation and brings about great and unnecessary confusion in administration. I think any program for improving the general medical welfare of children should avoid distinctions between the anatomical localization of their infirmities. Programs which separate a child's psyche from his body, his heart from his lungs, and a paralyzed leg from nutritional defects, are, in my opinion, fundamentally illogical and lead to dangerous habits of medical thinking although they do appeal to groups of workers with special and limited interests.

The broad criticisms of the bill that I have been so bold to make should not imply that I think the Federal government should not engage in activities to improve medical care. Even with the present limits of the science of medicine, there is a wide gap between what is known and what is generally applied. Instead, however, of a project attempting blindly with one sweep to wipe out medical indigence in the way so naively attractive to the medical laity, I believe legislation carefully worked out to attack first a variety of underlying problems should be devised. Legislation should be planned to stimulate improvement in medical knowledge, in medical education, and in distribution of physicians and health workers as a primary object, and not leave these all-important matters as secondary projects to be casually acted upon by state legislators more interested in the distribution of high sums for direct medical aid to individual voters. It seems to me, therefore, that the approach toward solving the fine ends described as the purpose of this bill must be made first by specific attacks on the problem of education and training.

Congress should provide facilities for direct financial aid to first class medical schools now existing and for others to be formed and make such aid provisionary to the maintenance of standards set by the entire group of medical schools themselves.

Congress should give direct aid to medical research and not only by setting up new agencies for specific projects but by broad grants to existing institutions. Medical education and research cannot be separated. The total amount spent for medical education and research should be multiplied many times.

There is great need for a large Federal fund to improve the distribution of medical care by contributing to individual and different programs the country over. Grants should be made for furthering the development of different schemes for improving medical practice where local organizations or communities desire it and can offer an intelligent plan. Federal aid for support of local prepayment or health insurance plans should be widely given, obviously along with some control of the scheme.

Not only should more hospitals be constructed, but far more important, support of teaching within those hospitals should be specifically made. Money for the support of resident physicians in many hospitals would often do far more good in improving medical care than direct financial aid to the patients.

Subsidies to physicians by country communities has often been successful in extending medical care to places where it is deficient, and such schemes should be given government support to attract physicians to communities where they seem to be most needed.

There are wonderful possibilities for improving the care of patients in the decentralization and extension of graduate medical education to small outlying hospitals to which the fostering and stimulating influences of a medical school could be extended. Many more good young physicians would spend five years in hospital training if they could be financially supported and if more teaching hospitals existed.

A great deal of experimentation in methods for reduction of the cost of medical care needs to be carried out. Subsidies for aid in the establishment of group clinics could quite properly be made as long as some control was made over the financial arrangements so that

the grants could not be exploited for the benefit of the physicians. Group clinics can be organized to give the finest medical care at greatly reduced costs. Where available, medical schools could logically be the focal point for organized group practice programs.

The functions of the present Children's Bureau which has accomplished so much should be greatly broadened and coordinated with other government departments concerned with public health. The identity of the Children's Bureau should not be lost but its place is obviously not in the Department of Labor. Its proper and logical function in carrying on problems of research, particularly those of necessarily national scope, have been almost completely ignored by Congress. It already has accomplished much in general education and could and should do far more. It is the obvious Federal agency to carry on the projects I have suggested as they relate to maternal and child care. The use of the Children's Bureau as an agency to direct the distribution of local medical care to individual patients seems very likely to diminish its effectiveness in more important fields.

Sincerely yours,

JAMES L. WILSON, M.D.

Brookline, Mass.
December 6, 1945

Dear Dr. Park:

As requested, I am sending you my conception of what the Pepper bill (S. 1318) would mean to the pediatrician now actively engaged in private practice should the bill be enacted into law.

To maintain the proper perspective we pediatricians must recognize: (1) that the objective of the Pepper bill is to provide medical care for over 40,000,000 "children" and, (2) that there are at this time 2,354 certified pediatricians in this country—a ratio of one certified pediatrician to 17,000 "children."

The actual medical care for the vast majority of children under the Pepper bill will be given by the family physician. This is the situation as it exists now and as it will continue for many years to come until a sufficient number of pediatricians are trained to assume the task.

The pediatrician has an important role in the successful operation of the Pepper bill, but this role is *not* to enter into competition with the family physician by offering to give medical care on the *per capita basis.*

The trained pediatrician can best serve the public and himself under the Pepper bill by rendering service at the consultant or specialist level. Since there will be too few certified pediatricians to fill the needs of the program even at this level, it is probable that, as in the EMIC program, a consultant will be defined as one who is a consultant in his specialty on the active staff of an approved hospital.

It is probable that many men in private pediatrics will continue to give service in well-baby clinics, well-child clinics, and out-patient departments as well as through visiting on hospital wards. These services under the Pepper bill will be paid for on a *per session basis.* We have no way of knowing what this remuneration will amount to, but we do know that the bill insists on a high quality of medical care through adequate remuneration. The individual state's health agency will determine these fees after consultation with the state's professional advisory committee.

If the pediatrician wishes to participate in the program as a consultant, he will receive a consultant's fee only if the attending physician requests the consultation and executes the appropriate forms. We do not know what the fees will be under the Pepper bill, but in the EMIC program in Massachusetts a consultant received for an office visit,

$5.00; for a hospital visit when the consultant was on the staff, $5.00; for a home visit or visit to any other hospital, $10.00; for care of a referred infant during the first two weeks of life, a maximum payment per week for three or more hospital visits, $6.00. This method of payment constitutes *the fee-for-service system.*

The pediatrician in the program would probably care for many referred patients under the *per case system.* This system would pay the consultant or specialist a stipulated sum for the total service he would render a patient during a particular illness or because of a particular condition, usually within a stipulated period of time. We have no means of knowing what the schedule of fees for various types of cases will be. We do have the assurance that the remuneration will be adequate as determined by a professional advisory committee.

A group of pediatricians might contract with the state health agency to provide medical care as consultants, or one or more pediatricians may contract to give postgraduate teaching, and the *salary system* might, under certain conditions, be a desirable method of paying for such medical services.

The present draft of the Pepper bill provides medical service to *all* without a means test. If the present bill should become law we are naturally concerned as to what will become of the pediatricians' private practice. I do not know the answer to this important question, but I do not think that many of our patients who can afford otherwise will accept any but the highest type of service for their children, and I doubt if they would accept hospitalization for their children at the ward level with all that that implies.

I do not see how the bill could be passed without some reasonable means test being applied by the individual states. If this should prove to be the case I do not believe the operation of the bill would injure the private practice of pediatrics.

In summary, I believe the pediatric specialist under the Pepper bill should serve at the consultant or specialist level only. I do not believe the bill would diminish the demand for private pediatric care by those who can afford to pay—particularly if a means test is included. The private pediatrician would continue to work in clinics and outpatient departments and on the hospital wards as he does now—the only difference being that he would have the novel experience of being paid for his services instead of giving them free.

Yours very sincerely,

STEWART H. CLIFFORD, M.D.

News and Notes

Dr. Milton J. E. Senn will deliver the fourteenth annual series of the Benjamin Knox Rachford Lectureships in Cincinnati on Tuesday evening, February 5, and on Wednesday evening, February 6, 1946, at 8:15 P.M. in the auditorium of the Children's Hospital Clinic and Research Building. The subjects of his lectures will be "The Relationship of Pediatrics and Psychiatry" and "Opportunities for Psychotherapy in Pediatric Practice."

Dr. Hart E. Van Riper, formerly with the Children's Bureau and later at the Jackson Memorial Hospital in Miami, Fla., has been appointed Assistant Medical Director of the National Foundation for Infantile Paralysis, Inc.

The Pediatrician and the War

The following promotions have been reported to the JOURNAL:

Army

Major J. Hugh Lewis, Wyandotte, Mich., to Lieutenant Colonel
Major Oscar B. Markey, Cleveland, Ohio, to Lieutenant Colonel
Captain William B. Nevins, East Orange, N. J., to Major
Major A. W. Pinkerton, Lima, Ohio, to Lieutenant Colonel

Navy

Lieutenant Commander Howard J. Morrison, Savannah, Ga., to Commander
Lieutenant Commander Morris Steiner, Brooklyn, N. Y., to Commander
Lieutenant Commander James H. Wallace, Oak Park, Ill., to Commander

The following Fellows have been released from military service:

Dr. Arthur F. Abt, Chicago, Ill.
Dr. Bernard Benjamin, Brooklyn, N. Y.
Dr. Montgomery Blair, Jr., Washington, D. C.
Dr. John B. Burns, Binghampton, N. Y.
Dr. Edwin R. Cole, Sacramento, Calif.
Dr. Wyman C. Cole, Detroit, Mich.
Dr. Richard G. Elliott, Lexington, Ky.
Dr. Ernest Freshman, Oneida, N. Y.
Dr. Paul Herzog, Kenosha, Wis.
Dr. John P. Hubbard, Washington, D. C.
Dr. Herman Landon, Chicago, Ill.
Dr. J. Hugh Lewis, Wyandotte, Mich.
Dr. Gordon Manace, Toronto, Ontario
Dr. Edgar F. Martmer, Detroit, Mich.
Dr. J. Keller Mack, Springfield, Ill.
Dr. Halcuit Moore, Dallas, Texas
Dr. Masters H. Moore, Tyler, Texas
Dr. Robert H. Moore, Dallas, Texas
Dr. Councill C. Rudolph, Coral Gables, Fla.
Dr. Harry Strongin, Brooklyn, N. Y.
Dr. Abraham Tow, New York, N. Y.
Dr. Tyree C. Wyatt, Syracuse, N. Y.

Book Reviews

Virus as Organism. Frank MacFarlane Burnet, Cambridge, Mass., 1945, Harvard University Press, 134 pages. Price $2.

Dr. Burnet is widely known as an authority on virus diseases and as Director of the Eliza Hall Institute of Research in Pathology and Medicine of Melbourne, Australia. The present book was presented as the Edward K. Dunham Lectures for the Promotion of Medical Sciences at Harvard University in 1944 and deals with the broader aspects of virology and virus disease as well as with certain selected diseases, such as herpes simplex, poliomyelitis, psittacosis, smallpox, yellow fever, and influenza, with special reference to their ecological aspects. The first two chapters deal with reproduction, variation and survival of viruses, and with evolution and change in virus disease. It is interesting to find that Burnet finds it necessary in the case of viruses, as Pasteur did so many years ago, for bacteria to combat the theory of spontaneous generation. The occurrence and importance of heritable mutations in viruses which lead to changes in virulence and severity of epidemics are stressed. Dr. Burnet's comments on the epidemiology of poliomyelitis were of great interest to this reviewer, especially his observations in Melbourne that some fairly direct chain of contact between *children* could nearly always be traced, and that there was no evidence of carriage of infection by adults.

This book will be of value to all who are interested in the clinical and epidemiological problems as well as in the fundamental principles of virus infection. It is not only authoritative, but also very readable.

H. K. F.

Paper in This Issue

Due to conditions beyond the control of the editors and publishers, this issue of the JOURNAL is printed on uncoated paper.